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THE RELATION OF VASCULAR DISEASE TO THE HYPERTENSIVE STATE*

II. The Adequacy of the Renal Biopsy as Determined from a Study of 500 Patients

BENJAMIN CASTLEMAN, M.D.,† AND REGINALD H. SMITHWICK, M.D.‡

BOSTON

IN APRIL, 1943, the anatomic findings observed in renal biopsies removed from 100 hypertensive patients subjected to bilateral dorsolumbar sympathectomy were reported.[1] The biopsies were graded according to the severity of the vascular disease without knowledge of any clinical data about the patient, and it was found that there were enough differences in the degree of vascular disease to classify the group into five grades of advancing severity (Grades 0, 1, 2, 3 and 4). In this first series 7 per cent of cases were Grade 0, 21 per cent Grade 1, and 25 per cent Grade 2 — that is, 28 per cent and possibly 53 per cent of the cases showed renal vascular systems so slightly damaged that it seemed unlikely that the blood flow could have been embarrassed sufficiently to be the one factor responsible for the hypertension. We therefore concluded "that in many of these cases and probably others the hypertensive state antedated the renal vascular lesions, which once established, probably aggravated the hypertension."

Since the publication of this paper, those who believe that renal vascular disease antedates the hypertensive state have objected that a small biopsy is not an adequate sample of the entire kidney and that no definite conclusions should be drawn from these biopsies.[2] We admit that in some cases the biopsy may not have been truly representative of the entire kidney, although an attempt was made to select a region that seemed on gross inspection an accurate sample. It is true that the biopsies are small, averaging 6 by 5 by 4 mm., but each microscopical section contains about fifty cross-sections of arterioles and small arteries. Furthermore, although vascular disease may be segmental in the large vessels and although not every arteriole is necessarily involved in kidneys removed at autopsy from hypertensive patients, arteriolar disease, when present in a kidney, is by and large a generalized process. It is perhaps possible in a small series of cases to strike a biopsy that is not an adequate sample, but it does not seem likely that this could have occurred in a series of 500 patients, which forms the basis for this report.

Table 1 shows the distribution of the grades of renal vascular disease in these 500 patients. The percentage of cases of Grade 0 and Grade 1 was a little smaller than that in the first series of 100 patients: 23.4 as compared with 28.0 per cent, and 45.6 per cent if one includes the Grade 2 cases, which really have very little arteriolar disease. Thus, 45 per cent of this series of 500 patients had so little anatomic change in their vascular systems that the blood flow through the kidneys could not conceivably have been reduced sufficiently to represent the sole factor in the production of the hypertension.

TABLE 1. *Distribution of Renal-Biopsy Grades.*

GRADE	NO. OF CASES	PERCENTAGE	
0	21	4.2	23.4
1	96	19.2	
2	111	22.2	45.6
3	218	43.6	
4	54	10.8	
Total	500		

Added confirmatory evidence for the accuracy of our grading and for the adequacy of the biopsy is the fact that in 100 cases a biopsy was taken from each kidney and that in the large majority the grade of vascular disease was the same on both sides. In only 5 cases was there a difference of two grades; in 20, there was a difference of one grade; and in the rest (75 per cent), the grades were the same. These findings are in keeping with the known bilateral character of the renal changes when they occur, and also with split-clearance studies as carried out by Chasis and Redish.[3] These authors have

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The tables and charts were exhibited at the centennial meeting of the American Medical Association, June, 1947.

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shown that the decrease in the rate of glomerular filtration and effective renal blood flow in hypertensive patients is shared equally by the kidneys: "These results indicate that the destruction of renal parenchyma progresses equally in the two kidneys in hypertensive disease." Forty of the 100 patients with double biopsies had minimal or no vascular disease on each side. This large percentage of Grade 0 and 1 vascular disease is probably due to the fact that as the years have gone by we have gradually come to see hypertension in its earlier stages and in younger patients. It seems to us that this finding of minimal vascular change in 40 per cent of this series is quite significant because the chances of missing real vascular disease twice are very unlikely.

Although it is fairly well established that the majority of hypertensive patients do not have renal impairment as measured by the phenolsulfonephthalein test, the finding that those with the more severe vascular disease in their renal biopsies had a decreased renal function and those with minimal vascular disease good renal function would provide additional support for the adequacy and accuracy of these biopsies. Renal function was measured by the phenolsulfonephthalein test in this series (Table 2). Sixty-four patients, or 12.8 per cent, had poor renal function, and when these cases are divided into their respective renal-biopsy grades it is quite obvious that most of them represented definite vascular disease. Ninety-two per cent had either Grade 3 or Grade 4 biopsies. At the other end of the scale, those with Grade 0 or Grade 1 renal biopsies, there were 117 patients, 84 per cent of whom had excellent renal function. When this correlation is charted (Fig. 1), the distribution of normal renal function among the renal biopsies in the first 100 cases was confirmed in the larger series of 500 cases.

TABLE 2. *Correlation of Renal Biopsies with Renal Function.*

GRADE	NO. OF CASES	RENAL FUNCTION			
		NORMAL	MODERATE REDUCTION	SHARP REDUCTION	
0	21	84.6% { 20	1	0	
1	96	79	16	1	
2	111	76	31	4	
3	218	132	55	31	92%
4	54	9	17	28	92%
Totals	500	316 (63.2%)	120 (24.0%)	64 (12.8%)	

Often, the severity of a patient's hypertension is based on the appearance of the eye-ground changes. We therefore believed that it would be interesting to compare the vascular changes in the retina with those in the renal biopsies. Table 3 shows that there is some correlation, especially in the very low and very high grades. For example, in 48 of the 66 (about 70 per cent) of the patients with Grade 4 retinal changes — changes that most clinicians consider diagnostic of malignant hypertension — renal biopsy revealed Grade 3 or 4 vascular disease. Likewise, about two thirds of the patients with Grade 4 renal biopsies had Grade 3 or 4 retinal change (37 out of 54). In the cases with Grade 0 or 1 renal biopsies, 78 per cent (91 out of 117) showed Grade 0, 1 or 2 retinal change. Although there were exceptions in all groups, in the Grade 2 and 3 renal biopsies all grades of retinal changes were rather well represented. This may be better visualized in Figure 2, in which the percentages of each of the retinal-vessel grades are calculated for each biopsy made. It is apparent that there is a definite correlation of the cases with Grade 0 and 1 eye grounds and those with Grade 4 eye grounds with the renal biopsies. In the middle

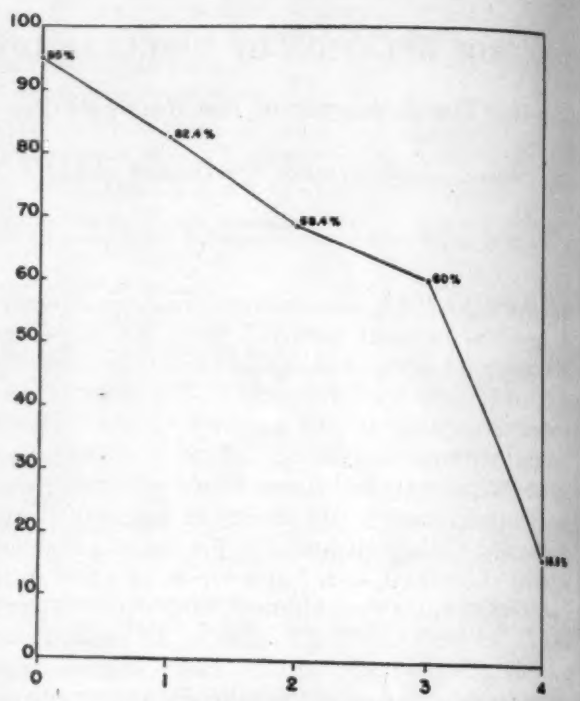

FIGURE 1. *Distribution of Normal Renal Function among the Renal Biopsies.*

TABLE 3. *Correlation of Renal Biopsies with Retinal-Vessel Changes.*

GRADE	NO. OF CASES	RETINAL-VESSEL CHANGE					
		GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	
0	21	2	11	2	5	1	
1	96	11	43	22	13	7	
2	111	13	36	22	30	10	
3	218	10	62	63	54	29	70%
4	54	0	7	10	18	19	70%
Totals	500	36	159	119	120	66	

group, those with Grade 2 and 3 eye-ground changes, all grades of renal vascular change were present.

Is there any correlation between the age of the patient and the degree of renal vascular change? Table 4 shows the age distribution of the 500 patients. The great bulk, almost 75 per cent, of them were between thirty and fifty. There were, however, 61 patients under thirty (Table 5), and it is interesting to note that 38 per cent had Grade 0 or 1 biopsies and if the changes in Grade 2 are included, 62.5 per cent of the younger patients had minimal vascular disease. These figures are even more significant when they are compared with the corresponding percentage among all age groups — namely 23.4 and 45.6 per cent (Table 1). It is very difficult, if not impossible, to know when a patient develops hypertension. Many have had their disease for years before it is discovered. Thus a patient of forty-five may well have had hypertension for ten years or more before it was first discovered, but a patient in the twenties, by the mere limitation of his age, has probably had it for a relatively short period. Assuming that hypertension is primary and renal arteriolarsclerosis secondary, a much milder degree of vascular change is expected in the younger group, and this is what was found.

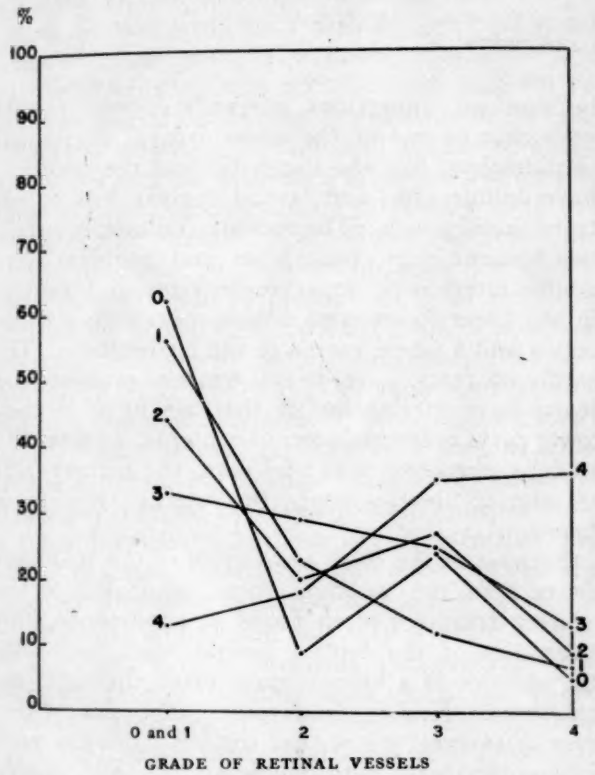

FIGURE 2. *Correlation of Renal-Biopsy Grades with Retinal-Vessel Changes.*

SUMMARY AND CONCLUSIONS

We believe that the material presented affords fairly conclusive evidence that the biopsies are adequate samples of their respective kidneys. The highlights of this evidence are as follows: First, approximately the same percentage of cases for each biopsy grade was present in a series of 500 cases as in the first series of 100 cases. Secondly, in 100 patients from whom biopsies were taken from both right and left kidneys, the grade of vascular disease was the same in 75 per cent of cases, and in only 5 per cent was there a difference of two grades (thus, in 95 per cent, the degree of vascular disease for all practical purposes was identical on both sides). Thirdly, in this group of 100 double biopsies, 40 patients had minimal or no arteriolar disease on each side. Fourthly, there was good correlation between the biopsy grades and renal function as measured by the phenolsulfonephthalein test in the entire series of 500 patients and in 20 patients when compared with renal plasma-flow values (previous study[4]). Fifthly, there was fairly good correlation between the biopsy grades and the retinal-vessel changes when applied to the lowest and highest grades.

TABLE 4. *Age Distribution.*

AGE yr.	No. of PATIENTS
10–19	8
20–29	53
30–39	141
40–49	224
50–59	72
60–61	2
Total	500

TABLE 5. *Distribution of Renal-Biopsy Grades among Patients Ten to Twenty-Nine Years of Age.*

GRADE	No. of CASES	PERCENTAGE		
0	5	8	38	62.5
1	18	30.0		
2	15	24.5		
3	15	24.5		
4	8	13.0		
Total	61			

Finally, of the 61 patients under thirty years of age, 62.5 per cent had minimal or no renal vascular disease.

For these reasons we believe that the biopsy material provides an adequate basis for conclusions regarding the degree of arteriolar disease in hypertensive patients. To repeat, 23.4 per cent of the biopsies were placed in Grade 0 or 1, and 22.5 per cent in Grade 2. Thus, 45.6 per cent of a series of 500 cases had minimal or no vascular narrowing. Since no one had objected to the accuracy of the observations in the biopsies, it must be concluded, as in

our previous report, that hypertension frequently exists in man without evidence of renal vascular disease or with insufficient evidence to explain the elevated blood pressure. Therefore, some other functional factor or factors that are primarily responsible for the hypertensive state and precede the appearance of renal vascular disease must exist in many cases.

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DOUBLE UTERUS WITH HORN MENSTRUATING INTO THE ABDOMEN

John B. Vernaglia, M.D.*

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A review of the literature has disclosed no case similar to the one reported below, which is that of a completely separated double uterus, both halves well developed, in which one uterus did not communicate with the vagina and menstruated into the abdomen. The situation was recognized at operation at the time of the patient's third menstrual period, and a hemi-hysterectomy was done. Later, the patient became pregnant and was delivered of a living child by cesarean section.

Congenital anomalies of the uterus are interesting but potentially serious conditions that warrant the careful consideration of every surgeon, gynecologist and obstetrician. They can cause dysmenorrhea, sterility, inflamed appendages, miscarriage, abnormal presentations, difficult or impossible delivery, uterine rupture, puerperal sepsis, placenta previa, retained placenta, post-partum hemorrhage and subinvolution. When there is atresia in the vagina or cervix, one may find, in addition to dysmenorrhea, hematocolpos, hematometra and hematosalpinx.

Embryologically the uterus and vagina are formed by the fusion of the two müllerian ducts in their distal or caudal two thirds. The cephalic third of each duct remains unfused and forms the fallopian tube on each side. These ducts appear during the sixth week of embryonic life, close to the more developed wolffian ducts. Their caudal segments move medially and become fused from below upward during the twelfth to the fourteenth week and form one tube, the uterus, cervix and vagina. Lack of complete fusion and disappearance of the intervening septum, at any point from below upward or throughout the length of the two ducts, explains most of the anomalies observed; the rudimentary development of one duct or of the cervical canal of one side accounts for the remainder. Nonfusion occurs normally in lower mammals, so that Blair–Bell suggests the use of the term "atavism" in preference to "malformation," because an anomalous uterus conforms exactly with that of one of the lower orders. Marsupials or didelphys, like the kangaroo and the opossum, have double uteri and lateral vaginas with a central vaginal pouch. The rodents (rabbits, squirrels, rats, guinea pigs, porcupines and gophers) have double uteri with separate cervixes and vaginas in the lower forms, and double uteri with a single cervix and a single vagina in the higher forms. The carnivora (cats, dogs, bears, weasels, raccoons and seals) have uterine bodies that are fused in their lower parts to form a bicornuate uterus. In primates, such as monkeys, apes and man, the highest form of uterine development, the uterus simplex, is found.

Because of the close association of the müllerian ducts with the wolffian ducts, anomalies of the urinary tract are often found in conjunction with anomalies of the female genital tract, especially the absence of a kidney, more often the right, according to Findley[1] and most authorities. However, Eismayer[2] states that the left kidney is more frequently absent with double uterus. Also, double anus, double bladder, presence of a cloaca and incomplete rotation of the colon (Sweet[3] and Benjamin and Danforth[4]) have been reported.

The various types of uteri are illustrated in Figure 1. A simple classification of malformations of the uterus and the vagina is that of Jarcho,[5] which is a simplification of that of Kaufmann.[6] This classification identifies seven types: uterus didelphys; uterus duplex bicornis bicollis; uterus bicornis unicollis; uterus septus; uterus subseptus; uterus arcuatus or cordiformis; and uterus unicornis. The first can occur with double vulva and should not be called "uterus pseudodidelphys" but rather "uterus didelphys cum vulva duplice," according to Jarcho.[5] A double vagina is present almost always, in the first type and often in the second. An even simpler classification of uterine anomalies, which recognizes only four main types and is much like classifications used by Royster[7] and also by Sichel,[8] is as follows: uterus didelphys

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— usually with septate (double) vagina; uterus bicornis, including bicornis bicollis (often with septate [double] vagina) and bicornis unicollis; uterus septus, complete and incomplete; and uterus unicornis.

The arcuate or cordiform uterus is merely a depression in the fundus of a normal uterus and is hardly worthy of a separate classification, though it may cause complications in pregnancy, labor and the puerperium. This classification is also essentially similar to that of Strassmann.[9]

The most serious complication of all these uterine malformations is the occurrence of pregnancy in a rudimentary or well developed horn that has no communication with, or a deficient cervical canal communicating with, the other uterus or the vagina. Pregnancy may occur in such a uterus by external migration of the spermatozoon or impregnated ovum. Rupture will occur at about four to six months with even more profuse hemorrhage than that from rupture in tubal pregnancy; death usually occurs ten to fifteen minutes after rupture in about 90 per cent of cases (De Nicola and Petersen[10] — in 88 per cent of cases according to Mundell[11]). The case reported below was such a situation, discovered before pregnancy had occurred. Rarely, the fetus in such a pregnancy dies and becomes mummified. Scott and Forman[12] reported twin fetuses retained in a horn of a bicornuate uterus for twenty years. At operation, a pregnant uterine horn can be distinguished from a tubal pregnancy if the operator identifies the round ligament lateral to the mass. Also, the other uterine horn is found to have a tube and ovary on its lateral side only. In Mulsow's[13] case (1945) rupture of a pregnant rudimentary horn occurred at five months, with death in fifteen minutes. Mulsow, in a review of the literature since 1911, could find reports of only 9 cases of pregnancy in a rudimentary horn. De Nicola and Petersen[10] reported a pregnancy in a rudimentary horn in 1947 and cited a case from India by Waters (1944), which had not been mentioned by Mulsow. Fortunately, an incorrect diagnosis of a tubal pregnancy is usually made, and the rudimentary horn is discovered at operation; otherwise, the condition is discovered at autopsy. The first recorded case of such a pregnancy is credited to Moriceau and Vassel by Wardlow and Smith.[14] Uteri with rudimentary horns are unsuspected because they do not have a vaginal septum. Injection of lipiodol followed by x-ray examination (uterosalpingography) will not reveal such a horn. In 1930 Grant and Rose[15] added a case to 6 recorded cases of bicornuate uteri with atresia and hematometra of one horn, the previous cases having been reported by Robinson[16] in 1910, Maclean[17] in 1911, Oliver[18] in 1912, Schwarz[19] in 1921, Nemes[20] in 1921 and Champel[21] in 1921. Several other cases have been reported without pregnancy in such uteri, the horn having little or no connection with the other uterus or the vagina, and causing hematometra with or without hematosalpinx. No case is recorded in which a well developed horn menstruated into the abdomen under the peritoneum, forming a pseudocyst distended with menstrual blood, as in the case reported below. According to Puddicombe,[22] Kehrer, in 1900, collected 84 cases of pregnancy in rudimentary horns. In 1916 De Lee[23] reported about 100 cases of pregnancy in a rudimentary horn, indicating that the condition is not extremely rare.

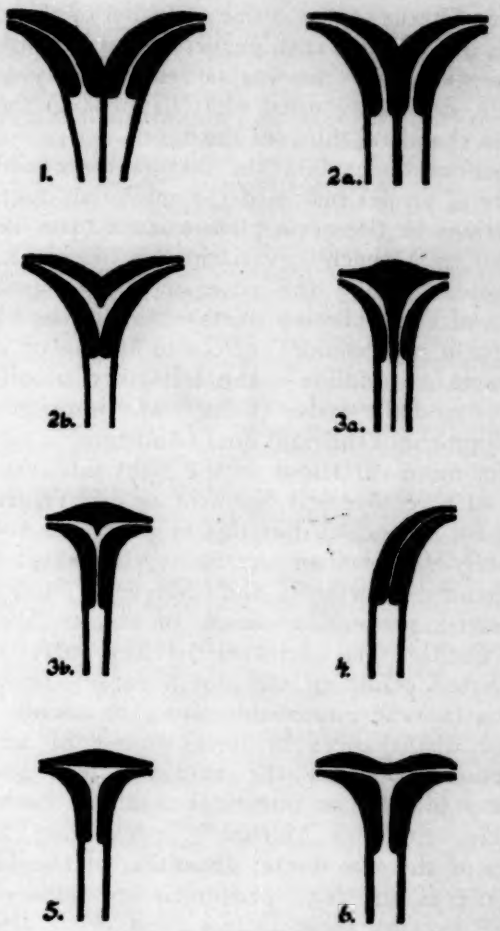

FIGURE 1. *Various Types of Uterus.*
1 = *uterus didelphys*; 2a = *uterus bicornis bicollis*; 2b = *uterus bicornis unicollis*; 3a = *uterus septus*; 3b = *uterus subseptus*; 4 = *uterus unicornis*; 5 = *uterus simplex*; 6 = *uterus arcuatus or cordiformis.*

In summary, therefore, the nonfused proximal thirds of the müllerian ducts normally form the two tubes, the fused middle thirds of the two ducts normally the single uterus and cervix, and the normal fusion of the distal thirds of the two ducts the single vagina. Various degrees of failure of fusion or of absorption of the intervening septum produce different types of doubling of the uterus, cervix and vagina. Uterus didelphys is caused by

complete failure of fusion of the middle thirds of the ducts, resulting in a double uterus and a double cervix. If the intervening septum remains in the distal thirds, there is also a double vagina. Since obliteration of the septum usually occurs from below upward, a double vagina is almost always present with uterus didelphys and often with uterus bicornis bicollis. Uterus bicornis is due to partial failure of fusion of the ducts in the middle thirds. The region of the cervix may or may not fuse, causing a single or a double cervix. With double cervixes the vagina is often double, as stated above. Uterus septus is due to fusion of the middle thirds of the ducts with persistence of the intervening septum, and the vagina may or may not be double, depending upon what happens to the septum in the distal thirds of the ducts.

Theories to explain the factors responsible for failure of proper fusion of the müllerian ducts are: variations in the germ plasma itself (von Winkle, quoted by Moench[24]); variations in biochemical environment during the time of development and fusion of the müllerian ducts — this is the likeliest theory in my opinion; errors in timing of arrival of ducts at midline — the left duct usually advances medially faster (Felix[25]) and interferes with development of the right duct (Anderson[26]), accounting for more variations on the right side; the presence of a rectovesical ligament or fold (Kussmaul, cited by Moench[24]), but this may be an associated anomaly rather than the cause; too short round ligaments (Newton[27] and Meyer[28]); too broad a pelvis, preventing union of ducts (Wardlow and Smith[14] and Schwarz[19]) — this may be an associated condition and not a cause; fetal peritonitis (a very improbable and rare cause); associated disturbances of development of adjacent structures, such as the wolffian ducts and the urinary bladder or intestinal tract, or both (von Winkle, cited by Moench[24]), preventing normal union of the two ducts; distention of the bladder and uterus and fetal peritonitis are ruled out by Felix[29] because these factors must occur after the fusion that forms the uterovaginal canal; Thiersch[30] blamed the greater development and separation of the wolffian bodies as the most plausible cause; Pick[31] blamed tumors, or interference by stray cells of müllerian tissue keeping the ducts apart. Very probably, other causes are involved, and different factors may be responsible in different cases.

Patients with double uterus are more fertile, according to Findley,[1] but have more abortions. They have more transverse and breech presentations, and also have more prolonged labors. They have poorer uterine musculature and more rigid cervixes, and they run the danger of incarceration of the nonpregnant uterus in the pelvis, where it can act as an obstruction to delivery. The nonpregnant complications of double uterus are dysmenorrhea and the so-called retention complications (Sweet[3]), hematocolpos, hematometra and hematosalpinx, depending upon the site of atresia. In 1926 Findley[1] collected 135 cases of double uterus and advised conservative management of pregnancy. Falls,[32] who stated that anomalies of the female genital tract occur in about 1 per cent of all women, stressed long labors, post-partum hemorrhage and placenta previa in these cases. He also emphasized an important fact, which bears repeating: the bladder is often carried back over the saddle of a bicornuate uterus in the rectovesical ligament, if present, where it can be damaged during cesarean section or hysterectomy. Strassmann,[9] of Berlin, who came to America to discuss Falls's paper in 1928, stressed the frequency of dysmenorrhea and inflamed appendages. He viewed pregnancy in a double uterus with the same apprehension as ectopic pregnancy, advocating emptying of the uterus and operation to form one cavity because of the frequency and danger of abnormal presentations, placenta previa, puerperal sepsis, retained placenta, post-partum hemorrhage, slow or obstructed labor and ruptured uterus. In 1896 Strassmann had first described his operation for conversion of uterus didelphys into a single uterus with a single cavity. At laparotomy, an incision is made running from fundus to fundus along the medial surfaces of the double uteri down into the internal os. Then the posterior cut edges are sutured to each other, as are the anterior edges up to and including the fundi. After closure of the abdomen, the vaginal septum and then the thick cervical septum are divided with a cautery.

In 1916 Rockey[33] reported a method of operation dividing the vaginal and the intrauterine septums, per vaginam, by leaving long clamps on the anterior and posterior margins of the septums for thirty-six hours, at the same time cutting between them with the cautery. He advised placing the patient in marked Trendelenburg position before the clamps are applied to the uterus in case the uteri are bicornuate, because of the danger of clamping bowel between them.

Owing to the great variety of anomalies, each case is an individual problem, and no set rules regarding treatment can be formulated. The less the deformity, the less the danger. The average uterus didelphys will deliver quite normally from either side provided the other uterus does not drop down and get in the way, or does not contain a tumor or another pregnancy, as has not infrequently happened. Quite a few cases have been reported of a second pregnancy and subsequent delivery (involving the other uterus) several or more months after pregnancy in, and delivery from, the first uterus. These cases have been cited by some as proving the occurrence of true superfetation, or the presence of two fetuses of different ages, not twins, owing to impregnation of two ova from different periods of ovulation. The removal of a

rudimentary horn is always advisable because of the danger of pregnancy. Whenever possible, surgical intervention for uterine anomalies should be conservative. Surgical measures based solely on the presence of an anomaly are seldom justified (Jarcho,[5] Granberry and Faust,[34] Smith,[35] Schauffler,[36] Sweet[3] and Tyler[37]).

Case Report

E. L. (M.H. 59904), a 12½-year-old girl, was admitted to the hospital on March 24, 1939, because of abdominal pain. The patient had had two normal periods, each with moderate pain lasting 4 days. The present period, beginning 4 days before admission and on time, was accompanied by headache and decreased appetite. Three days previously, she had complained of cramp-like pains all over the abdomen and had vomited once. There was an urgent desire to defecate, which was not relieved by enemas and a saline cathartic. The pain, the vomiting and the urgency to defecate became more marked. The pain was localized low in the abdomen, and became severe and steady. Enemas produced little feces, — mostly thick gray mucus, — and the mother noticed that the enema tip could not be admitted satisfactorily more than 3.5 to 5.0 cm. On the day of admission the mucus contained some dark blood. There were no symptoms referable to the cardiorespiratory, genitourinary or neuromuscular system.

The past history was irrelevant. The patient had been born after a forceps delivery. Infancy and childhood had been normal. She had had measles, chicken pox and whooping cough but no serious illnesses, accidents or operations.

The mother and father were living and well. The patient was the oldest of a family of four children, all of whom were living and well. There were no familial diseases.

Physical examination disclosed a well developed and well nourished girl, who complained of severe pain in the lower abdomen, more marked on the right. The skin was pink, dry and warm. The head, heart and lungs were normal. The abdomen was not distended. No organs were felt, and there were no hernias. Marked tenderness was noted in the lower abdomen without muscle spasm and without rebound tenderness. Rectal examination revealed a tender mass in front of the rectum, 7.5 to 10.0 cm. in diameter.

The temperature was 99°F., the pulse 80, and the respirations 22.

Examination of the blood showed a red-cell count of 5,060,000, with a hemoglobin of 82 per cent, and a white-cell count of 10,200, with 63 per cent neutrophils, 25 per cent small and 10 per cent large lymphocytes and 2 per cent eosinophils. Fluoroscopy with a barium enema demonstrated that the colon filled easily to the cecum, with normal regurgitation through the ileocecal valve. There was no tenderness over the cecum, which was movable and apparently not attached to the mass in the pelvis. There was a tender mass in the pelvis displacing the rectum to the left and apparently not attached to the cecum.

The patient was given intravenous saline solution, 5.0 mg. of morphine, and 0.4 mg. of atropine.

At operation, under ether anesthesia, she was placed in the lithotomy position and catheterized after preparation and draping of the perineum. On specular examination, the cervix was found displaced to the left and forward by a cystic mass. Aspiration of the mass with a needle revealed thick, dark blood. The patient was straightened out on the table, the abdomen was prepared and draped, and a right lower paramedian incision was made. Exploration revealed no fluid or free blood. The appendix was normal. Behind the bladder rose two uteri separated about 2.5 cm. at the lower ends and about 9 cm. at the fundi. Each uterus had one round ligament, and one tube and ovary on its lateral side. The right tube was thick, distended and congested. Retroperitoneally, anterior to the sacrum, was an ovoid, cystic, bluish mass, 7.5 by 10.0 cm., displacing the rectosigmoid to the left and the left uterus anteriorly and to the left. Obviously, the cervix, found displaced to the left on specular examination, belonged to the left uterus. Pressure on the right uterus increased the tension in the mass, confirming the suspicion that this uterus communicated with it and not with the vagina. The mass was tapped, and the same thick bluish blood was obtained as from the tap of the posterior cul-de-sac. There was no rectovesical ligament running from the bladder to the rectum and sigmoid, as frequently occurs with double uterus. It was decided that the right uterus was menstruating under the peritoneum, forming a menstrual pseudocyst. The peritoneum was incised over the front of the lower end of the right uterus, reflecting the bladder forward. A right hemi-hysterectomy and salpingectomy was done. The peritoneum was incised over the cystic mass, and it was easily dissected off the sacrum and rectum posteriorly and from the back of the lower part of the left uterus in front, without rupturing. Its cavity communicated with the cervical end of the right uterus through a tract about 0.4 cm. in diameter. The same thick bluish blood contained in the cyst distended the uterus and tube, producing a moderate hematometra and hematosalpinx. The patient made an uneventful recovery and was discharged on the 12th day.

The gross specimen consisted of a thickened tube, 8.7 cm. long, and a uterus, about 6.2 cm. long and 3.7 cm. across its widest point. One side was perfectly smooth. The uterus tapered down to a cervix with a canal, 0.4 cm. in diameter, which communicated with a pear-shaped saccular structure, 10.0 cm. long and 6.2 cm. wide. The uterus, the tube and the saccular structure contained thick old blood. The endometrium was markedly thickened and hemorrhagic.

Microscopical examination showed the tubal wall to be thickened and infiltrated with round cells. Sections of the uterus were not remarkable except that the endometrium was markedly thick and contained tortuous hyperplastic endometrial glands. Sections through the wall of the saccular structure showed it to be composed of fibrous tissue. The inner surface was covered with red cells. In one area the cyst was lined with tissue that had the appearance of endometrium. The adjacent tissue showed some old hemorrhage characterized by the deposit of hematoidin and hemosiderin. Histologically, the tissue was consistent with an endometrial implant. There was no evidence of cancer or tuberculosis.

The diagnoses were bicornuate uterus, hyperplastic endometritis, endometrial implant and chronic salpingitis.

After this episode the patient enjoyed good health except that she had painful periods, and in June, 1944, the right ovary was removed because it had become large, tender and cystic. At the same time, the appendix was removed, and several cysts of the left ovary were resected. The left tube was found patent. The patient married in October, 1946. She became pregnant and during the last month of pregnancy developed considerable lower abdominal pain, with tenderness and tenseness of the uterus. On April 30, 1948, 3 weeks before term, she also developed some vaginal bleeding. Because of the danger of rupture of the uterus, cesarean section was performed.* At operation, the uterus was tense and thin walled. On the front wall of the distended uterus ran five large veins, each 0.6 cm. in diameter, which converged low on the left side of the uterus. The lower two, which lay in the line of the incision, were tied off on either side to prevent unnecessary bleeding. A 4½-pound male baby was delivered, and the placenta showed some partial premature separation. Both mother and baby have done well.

Summary

The subject of uterine anomalies is reviewed, with special reference to embryology, classification, etiology, complications and treatment.

A simplified classification is presented.

What is believed to be the first reported case of double uterus with one uterus not connected with a vagina and menstruating into the abdomen, retroperitoneally, is presented. Hemi-hysterectomy was done, and this patient later bore a child.

Pregnancy in the rudimentary horn of a double uterus is stressed as even more dangerous than an ectopic pregnancy, and the diagnosis is more difficult.

Conservative surgical treatment is emphasized.

*The section was performed by Dr. Emilio D'Errico, of Medford.

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THE USE OF DIBENAMINE IN PHEOCHROMOCYTOMA*

Report of a Case

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THE adrenolytic drug dibenamine hydrochloride (dibenzyl-beta-chlorethyl amine hydrochloride)§ is presented as a diagnostic aid when the presence of a pheochromocytoma is suspected and as a therapeutic agent once the diagnosis is confirmed.

The preoperative diagnosis of a pheochromocytoma is based on the clinical picture, retrograde pyelograms and perirenal air studies. But none of these criteria are specific. In the following case dibenamine apparently blocked the effects of a pheochromocytoma by its adrenolytic action. Thus, the drug affords a more specific test in the diagnosis of a pheochromocytoma.

Method of Administration

The patient was given an intravenous infusion of dibenamine hydrochloride. The dosage was 7.0 mg. per kilogram of body weight. This was diluted in 300 cc. of 5 per cent glucose in physiologic saline solution. For its administration a Y-infusion set was used. One arm was attached to the bottle containing the dibenamine, and the other to one containing 5 per cent glucose in physiologic saline solution. The infusion was started with the glucose in saline solution, and then was switched to the dibenamine, which was administered over a period of one hour to lessen the possibility of toxic reactions.

Case Report

On September 11, 1947, M.P., a 51-year-old woman, was admitted to the hospital for the second time, complaining of attacks of precordial and abdominal pain, headaches, nausea, and diaphoresis.

The past and personal histories were noncontributory. The present illness had begun 21 years prior to admission, when the patient first experienced intermittent mild attacks of right-sided abdominal pain, headache, diaphoresis and nausea. They came on suddenly without any known precipitating factor, and even woke her at night. The pain spread from the abdomen superiorly to produce a severe, crushing headache. The duration of the attacks varied from a few minutes to days. Twelve years previously she had been

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admitted for the first time complaining of the attacks of abdominal pain. These attacks were aggravated by food and relieved by induced vomiting. At operation a chronically infected gall bladder filled with small stones was removed. The abdomen was explored, but no other disease was noted. Four years prior to admission she first experienced precordial pain and blurred vision during attacks. For the past 4 years she had been greatly incapacitated. The attacks had occurred as frequently as three or four times a day.

Physical examination disclosed a pale, thin woman, who appeared 20 years older than her stated age. There was no orthopnea or dyspnea. The fundi showed marked arteriovenous nicking and thickening of the arteriolar walls, but no papilledema, hemorrhages or exudate. The lungs were clear. The heart did not appear enlarged. Normal sinus rhythm, with occasional extrasystoles, was present. A coarse Grade II apical systolic murmur was heard. Examination

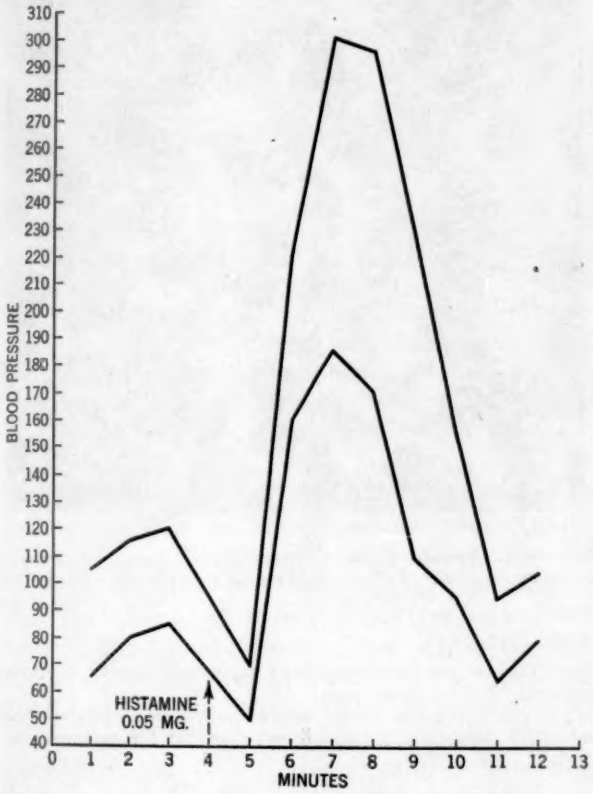

FIGURE 1. *Histamine Test Using 0.05 mg. of Histamine Base Intravenously.*

of the abdomen revealed only a well healed upper right rectus scar.

The temperature was 99°F., the pulse 96, and the respirations 18. The blood pressure was 130/100.

On admission and throughout the hospital course the urinalyses, blood counts, sedimentation rates and blood serologic findings were essentially normal. X-ray examination of the chest showed only moderate hypertrophy of the left ventricle of the heart. Repeated electrocardiograms, including multiple chest leads, revealed left-axis deviation and inverted T waves in Leads 1, 2 and 4.

A tentative diagnosis of hypertensive cardiovascular disease with coronary insufficiency was made. The patient was placed on nitrites and a rice diet for approximately 3 weeks, with no relief of symptoms. During the first 6 weeks she was observed to have a labile hypertension, the blood pressure varying from 250/150 to 130/80. Urine concentration and urea clearance tests were normal. Intravenous pyelograms were normal. Retrograde pyelograms were normal except that the right kidney appeared displaced somewhat laterally and inferiorly.

However, it was noted that there was a definite correlation between the daily hypertensive episodes and the symptoms. The paroxysmal attacks of hypertension accompanied by right-sided abdominal pain, precordial pain, headache and profuse diaphoresis seemed characteristic of an adrenalin-

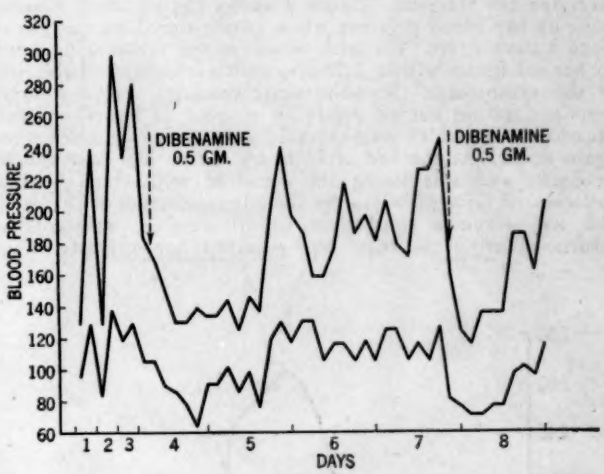

FIGURE 2. *Blood-Pressure Recordings, Demonstrating the Effect of Dibenamine Hydrochloride.*

producing tumor, the so-called pheochromocytoma. Accordingly, an intravenous histamine test, described by Roth and Kvale[1] as diagnostic of such a tumor, was performed. The results of this test, using 0.05 mg. of histamine base intravenously, are shown in Figure 1. After an initial drop, the blood pressure rose precipitously, associated with precordial and abdominal pain, headache, nausea and diaphoresis.

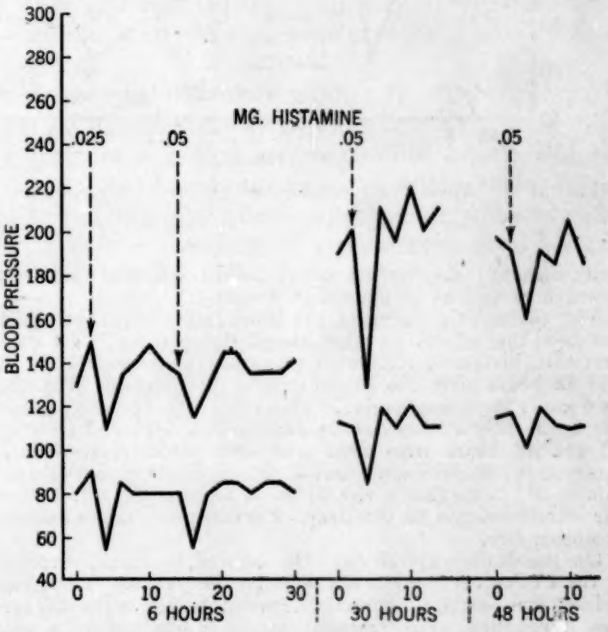

FIGURE 3. *Histamine Tests Following the Administration of Dibenamine Hydrochloride.*

These symptoms cleared as the blood pressure fell. This test was repeated with similar results. A cold pressor test was done, and a hyper-reactive blood-pressure response was elicited without the features of the attack previously described. Bilateral perirenal air insufflation with the con-

comitant administration of dye intravenously revealed a normal-appearing left kidney and adrenal area. The right kidney was displaced anteriorly by a large mass in the region normally occupied by the adrenal gland. The mass appeared to be a large adrenal tumor.

The patient was given dibenamine as outlined above. She experienced only transitory nasal congestion while receiving the infusion. Figure 2 shows the effect of dibenamine on the blood pressure when administered on two occasions 3 days apart. On both occasions the pressure dropped to normal limits within 2 hours, with an associated clearing of the symptoms. Blood-pressure readings, taken hourly, remained within normal limits for roughly 24 hours on each occasion, after which paroxysmal hypertensive episodes were again noted. At the end of 72 hours the patient had a mild headache and was losing the sense of well-being she had experienced immediately after the administration of the drug. She was given a third dose of dibenamine, with similar results. During this time she regained her appetite, slept

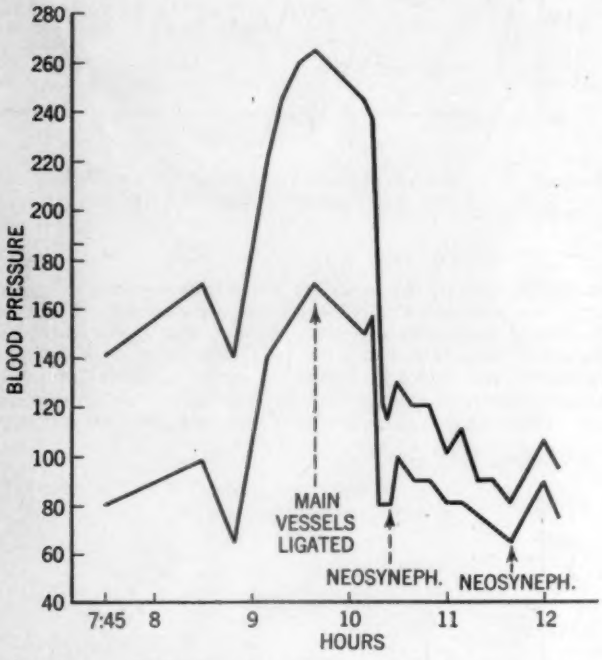

FIGURE 4. *Blood-Pressure Recordings during Operation.*

well without interruption from an attack and regained strength as well as 10 pounds of weight.

The adrenolytic action of the dibenamine apparently had nullified the effects of the pheochromocytoma. To confirm this, histamine tests were repeated at intervals of 6, 30 and 48 hours after the administration of the drug (Fig. 3). At 6 hours there was no rise in blood pressure, and the patient felt no ill effects from the histamine. Although the tests at 30 and 48 hours were done when the blood pressure had returned to hypertensive levels, the administration of histamine did not cause a rise to levels seen in the test before the administration of the drug. Furthermore, she remained symptom free.

On the 76th hospital day, Dr. George F. Hoch, director of the Urological Service, operated on the patient. The right kidney was normal. Directly superior to the right kidney was a rounded, semi-fluctuant mass, approximately 8 cm. in diameter. When the mass was dissected free, it ruptured, with the escape of tissue having the appearance and consistence of hyperplastic endometrium. The blood pressure dropped after the rupture (Fig. 4). Bleeding was controlled immediately by ligation of the pedicle of the mass. A drain was placed down to the ligated pedicle, and the wound closed. The patient was returned to her room in good condition.

On gross examination the tumor was found to be encapsulated and to contain soft, friable material, which was solid and without fibrous strands or stroma. Stained with potassium bichromate, the tissue turned dark brown. Microscopically, it was composed entirely of small cells closely packed in a loose connective tissue carrying blood vessels

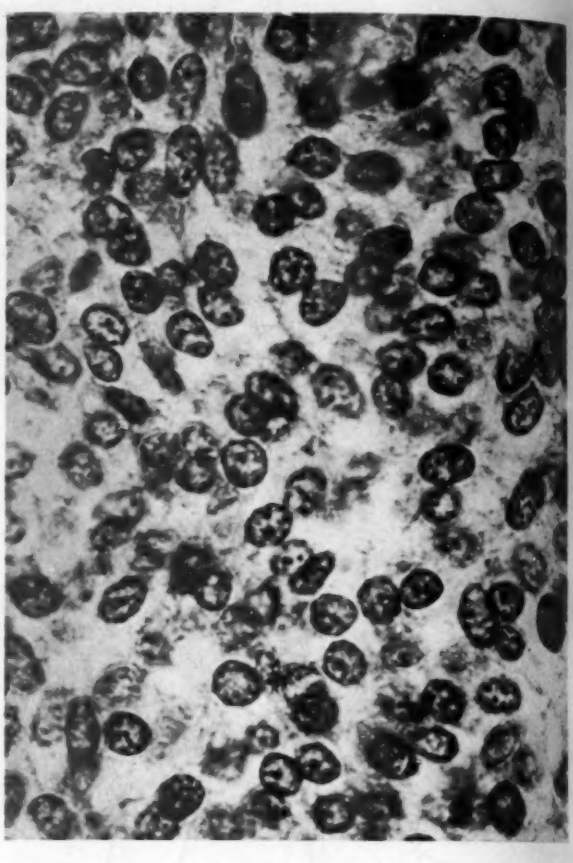

FIGURE 5. *Section from Tissue Treated with Bichromate, Showing Granular Yellowish Material between the Cells* (x900).

(Fig. 5). In the chromate-fixed tissue some cells contained granular, brown cytoplasm.

The postoperative course was uneventful except for a brief period of hypotension, which was controlled with neosyneph-

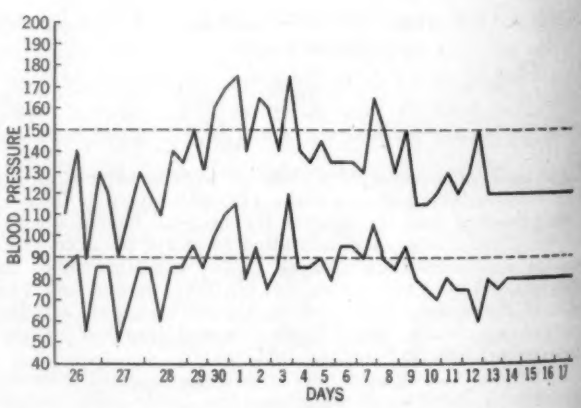

FIGURE 6. *Blood-Pressure Recordings after Operation.*

rin. During the period of early ambulation, the blood pressure rose to levels as high as 175/120 (Fig. 6). Subsequently the level fell and stabilized at 120/80. A glucose-

tolerance test was made to compare the results with the one performed preoperatively (Table 1). Preoperatively, a hyperglycemic curve was noted, whereas postoperatively the results showed a normal curve.

Postoperatively, a histamine test was repeated (Fig. 7). This caused neither any rise in the blood pressure nor any untoward symptoms.

On December 21 the patient was discharged complaining only of residual discomfort in the right flank. When last seen 5 months postoperatively she had remained well, and the blood pressure had continued within normal limits.

TABLE 1. *Preoperative and Postoperative Glucose-Tolerance Curves.*

TIME OF DETERMINATION	GLUCOSE-TOLERANCE TEST				
	FASTING	AT ½ HR.	AT 1 HR.	AT 2 HR.	AT 3 HR.
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
Preoperatively	119	144	203	161	61
Postoperatively	76	133	92	105	67

DISCUSSION

Once the paroxysmal attacks of precordial and abdominal pain, headache and diaphoresis had been correlated with the hypertensive levels of the blood pressure, the diagnosis was apparent, and yet unproved. Recent work on dibenamine hydrochloride[2] has shown that this compound is adrenolytic but not sympatholytic. This action seemed desirable from both the diagnostic and the therapeutic standpoint in the case presented above.

From the diagnostic standpoint the important finding was that the blood-pressure level remained within normal limits for twenty-four hours after the administration of dibenamine and furthermore that the symptoms were relieved for seventy-two hours. The blood-pressure level when the drug was administered was of no significance in affecting the success of the test. The histamine test was of definite value in proving the diagnosis, but had the disadvantage of initiating an attack. This added strain was undesirable in a debilitated patient. For the most striking results the histamine test should be done while the blood pressure is within normal limits. Recently, benzodioxane[3] has been reported as an adrenolytic drug of value in the diagnosis of pheochromocytoma. This drug, when used while the blood pressure is elevated, will lower the pressure for a period of fifteen minutes.

From the therapeutic standpoint dibenamine relieved the patient of her symptoms. Her appetite returned, and she gained 10 pounds in nine days. She slept well and appeared more rested. As a result she was prepared for operation more effectively.

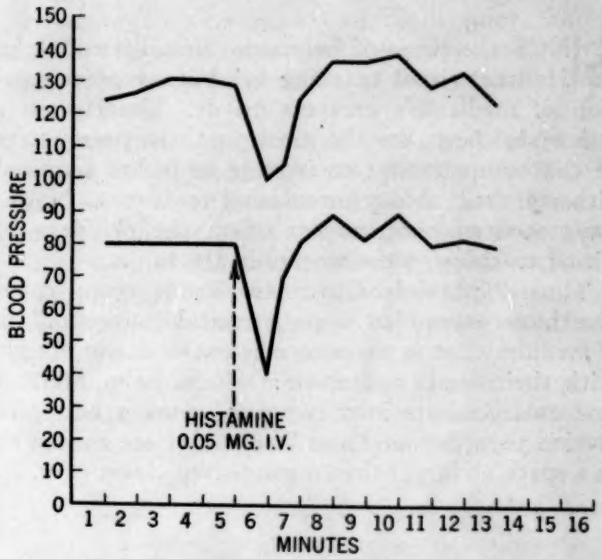

FIGURE 7. *Histamine Test after Operation.*

SUMMARY

The adrenolytic agent dibenamine hydrochloride was administered to a patient with a pheochromocytoma.

After the administration of dibenamine the paroxysmal elevations of blood pressure were eliminated for a period of twenty-four hours, and the patient was symptom free for seventy-two hours.

Dibenamine hydrochloride appears to be of value both in the diagnosis of a pheochromocytoma and in the therapy during preoperative preparation of the patient.

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THE PHOTOGRAPHIC MUSEUM*

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SINCE the times of Leonardo, Vesalius and John Hunter, visual teaching has been a preoccupation of medicine's greatest minds. Unfortunately it has also been, for the most part, the prerogative of that same group: to indulge in it has required either artistic ability or unusual resources. Nowadays modern photography offers the privilege of visual teaching to the worker in the ranks.

Thus, 7 physicians in nonacademic group practice have assembled a pathological "museum" in a medium that is at once efficient and compatible with their funds and space: 35-mm. color film. A few enlargements in viewboxes, viewing and projection paraphernalia and 7000 slides are contained in a space no larger than a good-sized closet (Fig. 1).

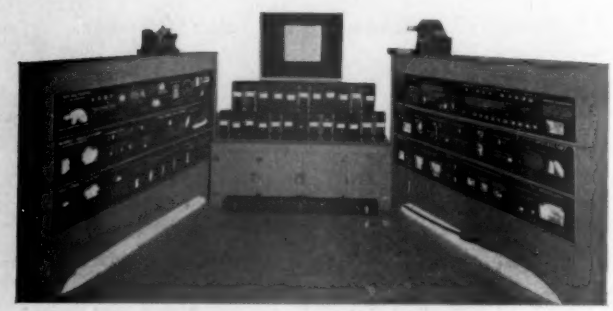

FIGURE 1. *A Pocket Museum.*

The largest — and least important — constituents are the lightboxes for enlargements. All other items — the projector, automatic projector, rolled screen, hooded daylight screen, 7000 filed 35-mm. color slides and (not illustrated) collapsible lightboxes for sheets of unenlarged slides — would fit into a large trunk.

The collection was built upon principles laid down some years ago and amplified here because of the growing interest in photographic museums[4–11] and because of the belief that some of the findings in a test case might be projected into more important endeavors.

The museum of gross specimens has two advantages over the photographic museum: specimens offer third dimension and the possibility of microscopical restudy. However, color transparencies give fair third-dimensional illusion — better than that of black-and-white prints. Then, too, specimens after being photographed can be stored inexpensively in formaldehyde tanks for later study.

The photographic museum has advantages of its own. Thus, in the Buffalo Museum of Science:

> First — It has been found that transparencies and photographs hold the interest when original objects do not. Second — In some cases transparencies of a complete object make an original fragment intelligible. Third — In many instances they divert the attention back to the original.[12]

Photographic color is truer than the color of preserved gross tissue. Color usually disappears from the preserved specimen in a year or so.[13] Color slides last several years: how many we do not yet know. Specimens shrink and distort.[14] In an audience, specimens must pass slowly from hand to hand. Photographs are projected, or transilluminated, for all at the same time. If 35-mm. film is used, 600 slides can be filed in the space required for 1 medium-sized specimen jar. Slide making is fast and efficient, while the preparation in color of actual tissue is time taking and puttery. Jars or watch glasses require frequent servicing, cleaning, refilling and resealing. The cost of preparing a gross specimen approximates three dollars, and that for taking and filing a slide nineteen cents. These are material expenses and include neither the cost of space and the salary for museum diener on the one hand nor the photographer's salary on the other. Without a biophotographer the photographic museum must remain, like ours, amateur.

The amateur — that is, the doctor — can with some study and effort take many of his own pictures.[2, 3, 15–17] He will meet a helpful welcome from the professionals of the Biological Photographic Association,[18] and he will find that composing pictures, like sketching, sharpens his eyes[19] and that his pictures will receive disproportionate praise from those whose photographic knowledge is a little scantier than his own. However, our kindest compliment, awarded some views of operative fields and recorded here with no pretense of modesty, was: "Who does your surgery for you?" The fact that we were elated when the best of many amateur pictures thus were mistaken for routine professional results is a measure of the difference between amateur and professional. Professional photography is one of the few remaining bargains in medical care. Martinsen[20] reported in 1940 that the average of 110 full-time and part-time biologic photographic departments employed 1.4 persons, occupied 730 square feet of floor space, cost $3146 yearly (of which 40 per cent went for materials) and used equipment valued at $3109.

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Museums that can afford it probably will use larger film, but unenlarged 35-mm. slides of small lesions are large enough to view by magnifying glass. Cardboard mounts[21] are available that hold several slides, so that one mount can illustrate various signs or stages of a disease and be accompanied by explanatory text. These mounts can be clipped upon inexpensive standard lightboxes. Series of filled mounts can be stocked in reserve and, if space allows, left on display.

Enlarged transparencies in color make better displays than 35-mm. film but necessitate especially constructed lightboxes. Lightboxes can be constructed like sectional bookcases[22] (Fig. 2). Front panels windowed individually for each series of enlargements and screwed to such boxes are interchangeable so that extras can be held in store. If large pictures or charts are to be shown, a single front panel two or more units tall can be mounted on two or more back units.

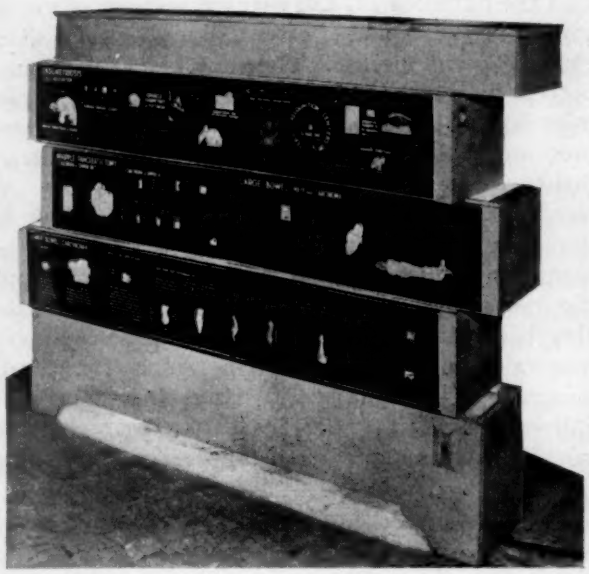

FIGURE 2. *Sectional Take-Down Lightbox.*

Enlargements and viewboxes take as much space as gross specimens in jars and cost even more. But it is assumed that the photographic museum will use only a small proportion of permanent, and therefore semi-immobile, displays and that its backbone will be a store of slides for projection.

The 35-mm. slide can be just as satisfactory — some,[21] including ourselves, prefer it in ordinary circumstances — as the 3¼-inch x 4-inch slide in projection. Small, hooded screens make color projection practical in lighted rooms. Automatic projectors,* operated by the visitor himself (Fig. 3), can project sequences of 50 slides. Sequences can be changed from week to week, and extra magazines kept loaded with those most in demand. The slide bank should be so cross-indexed that an attendant can project special sequences at request. For example, a visitor who inquires about lip lesions could be shown leukoplakia, mucous cyst, epitheliomas of varying grades of malignancy, hemangioma and chancre, preferably in conjunction with their microscopical sections, to which the film index can be keyed.

Comparative projection[23] has peculiar virtue: two or more projectors can demonstrate side by side the facies and the temperature chart; the gross and the microscopical appearances of a tumor; similar tumors of different grades of malignancy; contrasting graphs; a picture and a textual explanation; roentgenologic and operative appearances; and before-and-atters or, sometimes most useful of all, a normal with which deviation can be compared.

A contribution peculiar to the slide bank is the opportunity it offers of reaching beyond the walls of the museum into classroom, clinicopathological conference and staff or society meetings — that is, of bringing gross pathology to the man in practice. Clinicians are anxious to see gross disease, and color film is as logical a teaching tool in gross pathology as is the microtomic section in histopathology.

FIGURE 3. *Photography of the Operative Field.*

The contribution peculiar to color film is its ability to show *living* disease. Abnormal tissues, like normal, change with death, and the ordinary embalmed specimen bears no closer resemblance to living disease than does the embalmed body to the living man.

*Available from Spindler and Sauppe, Los Angeles, and Bausch and Lomb, Rochester, New York.

Other changes in tissue appearance occur before those of death: freshly excised tissue, although still living, wears an appearance that is but a caricature of the same tissue intact in natural surroundings. Compare an amputated part, for example a leg, with its remaining counterpart. The amputated leg is alive. Skin and bone would grow if grafted; blood would bind oxygen if transfused; muscles still contract upon stimulation. But the unpleasant object, however alive, is more specimen than leg. The blood is unoxygenated, dark. Muscular walls of arteries and arterioles have squeezed their contents onward into distended veins. Gravity has puddled blood in dependent areas. Redistribution of blood alters and redistributes color, for blood, as it is seen through tissue filters of varying thickness, density, refraction and pigmentation, is the source of most tissue color. Note the different tones of color in a square centimeter of your own skin and the uniformity of color in a corresponding piece of excised skin.

Alterations of blood and nerve supply change not only color but also form. After excision the spleen may shrink 30 per cent: splenic notches all but disappear. In the amputated leg, denervated muscles are flaccid. Devascularization and denervation alter texture, too, by changes in elasticity, in arteriolar and capillary pressures, and in the pressures of surrounding tissues. The facies of a person in simple syncope is a fair example of the metamorphosis caused by minor alterations in vascular and nervous supply. The excised specimen is a fainted specimen. Who would hang fainted ancestors on the walls of his home?

Usually the excised specimen also carries the marks of hands, instruments and sponges. Delicate lesions — for example, the serosal appearances in peritonitis — may be ruined even by gentle palpation with the moist, gloved finger. Recent studies of endometriosis[24, 25] suggest that an appreciable proportion of the large number of missed diagnoses in this common disease is paradoxic: that is, the diagnosis is unconfirmed *because* the lesion is excised. Lesions so striking that the surgeon spots them immediately upon opening the abdomen may have faded and been sponged into invisibility before the end of operation. Meigs[25] marked endometriotic lesions with pins so that the pathologist might know where to cut blocks. Truthful pictures of such lesions can be made only before they are handled, but there are today several cameras able to cope with most problems of in-situ photography.[2, 3, 26, 27]

The medical student, whose pathological concepts are conditioned by the pictures of pictures in texts, and even the internist and pathologist, accustomed to post-mortem appearances, may be less fussy than the surgeon about ante-mortem photography: some pathologists have surgical specimens sent to the laboratory in formaldehyde and never see living disease. But museums are not mausoleums, and to the surgeon and practitioner, who work with living disease, a museum is likely to appear only as alive as its material. Naturalists have shown us the way: they advanced from stuffed to caged animals, and from cage to natural habitat.

Conclusions

Photography has given the private practitioner a chance to teach. It may invigorate museums and revive the neglected science of gross pathology. Because color film is able to record lesions as they appear in vivo and because modern cameras can photograph many lesions in situ, it seems likely that the pathological and surgical sections of tomorrow's museum will be, essentially, a store of slides showing *living* disease. The slide bank can be supported by gross specimens preserved in bulk for microscopical restudy. In the large, endowed museum, slides would be supplemented by enlargements, paintings, drawings, working models and moulages, especially of lesions that cannot yet be photographed in situ. The slide bank can be implemented by apparatus that will not only demonstrate the museum's holdings within its own walls but also bring them outside to busy men in schools, hospitals and meetings. One such "practical" museum of living disease, assembled on a small and experimental scale, has shown that clinicians can be a museum's most appreciative audience.

10 Institute Road

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MEDICAL PROGRESS

SARCOIDOSIS (Concluded)*

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BOSTON

Anatomic arguments. The histologic resemblance of the sarcoid lesion to the "hard" tubercle produced by the tubercle bacillus under certain conditions cannot be denied. Certain animals, such as the rat, also react rather characteristically to this organism with productive noncaseating tubercles.[4, 228] However, identical histologic lesions can be produced in man by such varied agents as those of leprosy and syphilis, and even by beryllium compounds, and the various lesions of tuberculosis itself can be mimicked in every detail by other agents, such as silica.[229]

Although tubercles may apparently persist in recognizable form after the organisms that produced them have been destroyed,[191] they do not seem capable of persisting unchanged for long periods as many sarcoid lesions do. Experimental tubercles in the livers of rabbits, for example, have been observed to disintegrate rapidly and disappear once the organisms have been destroyed.[79] Even the lesion described by Kyrle[223] ran its course in three months — a considerably shorter period than many skin lesions in sarcoidosis.

The pattern of dissemination in sarcoidosis, although suggesting a hematogenous spread with lymphoid or reticuloendothelial localization, is somewhat different from that of miliary tuberculosis. It has been pointed out, for example, that although myocardial tuberculosis is quite rare, such localizations appear much more commonly in sarcoidosis, whereas the reverse appears to be true of intestinal, adrenal and meningeal localizations. The pattern of lymph-node involvement in sarcoidosis and tuberculosis also tends to differ. Unfortunately, in view of the limited number of thorough autopsies, the exact incidence of such localizations is not certain, and clinical findings are rather unreliable criteria. Furthermore, the marked tendency of the disease to progress and regress in irregular fashion may result, in many cases, in a very inaccurate impression of actual localization. In any event, if the disease is a form of tuberculosis, it must represent the effect of an unusual organism, an unusual host state, or both, and under these circumstances, an unusual distribution might not be especially remarkable.

Finally, at least 10 per cent of patients with sarcoidosis develop ordinary caseating tuberculosis.[4, 8] A number of authors have reported transitions between the two types of lesions at autopsy[43, 69, 85, 230] or even disappearance of sarcoid lesions with the onset of caseation.[7, 95] On the other hand, there have been reports in which both types of lesions coexisted and appeared entirely distinct.[231] Such findings are difficult to evaluate, especially in view of the fact that a number of diseases such as leprosy and Hodgkin's disease may also be complicated terminally by active tuberculosis.

Immunologic arguments. It seems highly unlikely that the high incidence of weak or negative reactors to tuberculin can represent simply a lack of infection with the tubercle bacillus. In some series drawn from urban populations, the incidence is distinctly higher than the expected incidence in a comparable population group.[38] Furthermore, many cases show evidence of previous tuberculous infection. Such infection has been demonstrated not only in the form of pulmonary calcifications, which can be caused by agents other than the tubercle bacillus, but also as unmistakable primary complexes revealed at autopsy.[191]

If sarcoidosis is caused by the tubercle bacillus, it becomes necessary to postulate a specifically altered tissue state whereby the organisms can be rapidly destroyed and tubercles formed in the absence of tuberculin hypersensitivity demonstrable by either cutaneous or focal reaction. This is the state to which Jadassohn gave the rather paradoxical term "positive anergy" to distinguish it from the "absolute anergy" of the uninfected and the "negative anergy" of the cachectic person, and it has been discussed in detail by Sulzberger[222] and Lemming.[210] A number of theories have been

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developed in an attempt to explain this peculiar immunologic situation.

Spontaneous desensitization. It has been known for a long time that skin sensitivity to tuberculin may be gradually lost — even to a degree whereby the subject may fail to react to large doses.[232] Tuberculin sensitivity induced by BCG vaccination may also be lost.[233, 234] Desensitization occurs spontaneously in animals[235] and has been produced experimentally by injections of tuberculin without impairment of immunity to reinfection.[236, 237] It has been postulated, therefore, that a similar effect may be produced by repeated hematogenous dissemination of tubercle bacilli as might be the case in sarcoidosis.[120]

If this theory is so, a reinfection with tubercle bacilli might be expected to cause a return of hypersensitivity as has been demonstrated experimentally.[235, 238, 239] As a matter of fact, it has occasionally been noted that a previously negative tuberculin test has become positive during or after a sanatorium stay or in the course of development of caseating tuberculosis in a sarcoid patient.[7, 230] In a number of cases the altered reactivity has preceded the clinical manifestations of active tuberculosis by several months.[88] On the other hand, vaccination of sarcoid patients with BCG, even in two or three times the usual dose, may fail to produce a positive tuberculin test,[210, 211] or may produce only a delayed or slightly positive reaction[226, 240]; experimental reinfection of desensitized animals with very small numbers of attenuated or nonpathogenic acid-fast bacilli, however, has also resulted in marked delay or suppression of the development of hypersensitivity in comparison with controls,[238, 239] and repeated injection of attenuated bacilli into guinea pigs has caused some of them to lose their hypersensitivity while retaining their resistance.[241] These findings constitute no convincing proof but are at least sufficiently challenging to warrant further investigation.

Anticutins. Substances capable of neutralizing the skin sensitivity to tuberculin (anticutins) or enhancing it (procutins) have been demonstrated in the blood serum of patients with sarcoid lesions associated with lack of tuberculin hypersensitivity.[222, 228, 242] Similar neutralizing substances have been demonstrated in the rat,[228] an animal that fails to develop tuberculin hypersensitivity after infection. The significance of the latter, however, has been questioned on the grounds that the rat is constitutionally resistant to hypersensitivity reactions in general.[243]

Pinner, Weiss and Cohen[244] have recently studied these substances in a small number of normal, tuberculous and sarcoid persons. Anticutins were demonstrated in only 4 (36 per cent) of 11 patients with sarcoidosis; they were also demonstrable in 18 per cent of various groups of tuberculous patients — the highest percentage being in a group of 23 such patients with a low degree of hypersensitivity — and in 3 to 9 per cent of normal subjects. Procutins were found in another 36 per cent of the sarcoid patients. The authors were forced to conclude that anticutins played no significant immunologic role in sarcoidosis. Other authors have also failed to demonstrate them.[44]

Local fixation of antibodies. This theory, supported by Leitner,[55, 177] suggests that in sarcoid patients the antigenic substances of the tubercle bacillus fix antibodies locally at their sites of origin (the reticuloendothelial system), and thus skin sensitization is prevented. Such a concept assumes the presence in tuberculosis of antibodies with secondary tissue-cell sensitization, but this has not yet been proved.

Epidemiologic arguments. The majority of sarcoid patients give no history of unusual exposure to tuberculosis[10, 24] although there is disagreement on this point.[86] In the various families and sibling pairs in which the disease has occurred, however, a significant incidence of tuberculosis has been recorded.[49, 53, 56] Such cases are interesting and possibly significant, but so far represent too small a proportion of the total cases reported to permit accurate evaluation. It is impossible at present to divorce the factors of infection, environment and constitution, or to establish for certain whether or not the incidence of tuberculosis in these groups differs in any way from that in other comparable groups.

In summary, the case for tuberculosis rests largely on negative, circumstantial or controversial evidence, a point freely admitted by at least one of its supporters.[191] The tubercle bacillus has not, however, been excluded as a possible etiologic factor. The validity of the few positive bacteriologic findings remains a crucial point, and here the issue has reached a stalemate. If, as is often the case, the identification of tubercle bacilli is accepted as *a priori* evidence that the case is one of tuberculosis and, therefore, not sarcoidosis, it is difficult to see how the point can be proved from a bacteriologic standpoint at least.

It has been suggested that other forms of tubercle bacilli, or related bacilli, are the responsible agents, but, in general, the arguments on both sides are the same as those already presented. Bacilli of the bovine[7, 245] and avian[246] strains have been reported in sarcoid lesions but, as in the human form, the majority of inoculations into susceptible animals has been negative. Immunologic studies have also provided little clue. Brooke and Day[247] tested 7

cases of sarcoidosis proved by biopsy with 18 different tuberculins, but noted no significant difference in reaction from 5 normal controls.

Leprosy

The occurrence of leprosy in a tuberculoid form that may be histologically indistinguishable from sarcoidosis[248, 249] has suggested to a number of authors that the lepra bacillus or a closely related organism is an etiologic agent.[250, 251] Further support has been lent to this view by the fact that in such tuberculoid forms, bacilli are so few as to be difficult or impossible to demonstrate by ordinary methods,[248, 252, 253] and that animal inoculations with lepra bacilli are invariably unsuccessful. Rabello[250] also notes that a torpid and discrete adenopathy analogous to that of sarcoidosis both clinically and histologically is frequently seen in such cases, and that characteristic pulmonary and osseous lesions may also occur, as well as tuberculin anergy. Cystic bone changes in the phalanges closely resembling those seen in sarcoidosis have also been described by others.[8, 134]

There seems little doubt that leprosy is capable of mimicking at least part of the sarcoid picture, and it seems quite likely that some cases reported are, in fact, leprosy. Pardo–Castello[248] is of the opinion that sarcoid disease due to leprosy is indistinguishable from any other form of the disease, and Boeck himself is reported to have diagnosed a case of tuberculoid leprosy as a cutaneous sarcoid.[254] Whether leprosy can reproduce the entire clinical and pathological picture of sarcoidosis is another matter, however, and is considered by a number of authors as highly unlikely.[255, 256] Furthermore, the tuberculoid forms of leprosy are almost invariably associated with the neural type of the disease[248, 257]; in such cases the peripheral nerves show direct invasion,[172] something that must be exceedingly rare in sarcoidosis if it occurs at all.

Some efforts have been made to analyze this problem on the basis of immunologic reactions. Weeks and Smith[258] performed skin tests on 10 proved cases of sarcoidosis. They found 6 to be negative to both lepromin and tuberculin, whereas 2 were positive to both. Of 5 other cases similarly tested by Harrell and Horne,[259] 2 were negative to lepromin, and 3 gave a faintly positive reaction considered nonspecific; of the latter, 2 were tuberculin positive as well. Thus, in practically all 15 cases, the results with lepromin either were negative or could be explained on the basis of a cross reaction with tuberculin, which has been demonstrated to exist by a number of investigators.[260–262] This is in marked contrast with the fact that, unlike the frequently weak or negative tuberculin reactions seen in sarcoid patients, the lepromin reactions in the tuberculoid (or sarcoid) forms of leprosy are strongly positive in 90 to 100 per cent of cases.[248, 252, 263] Fifteen cases are admittedly a small sample on which to base conclusions, but in view of these findings it seems highly unlikely that, in this country at least, the tuberculoid form of leprosy masquerades as sarcoidosis in any appreciable number of patients. In such cases, the lepromin test might be expected to prove a useful aid in diagnosis.[259]

Other Infectious Diseases

A number of granulomatous diseases known to be capable of wide dissemination have also come under suspicion, and several have been shown to exist in a sarcoid form. In all such cases organisms may be very difficult to find, and, as in tuberculosis and leprosy, both the prompt destruction of the organisms and the morphologic character of the lesions may be explainable by the same altered immunologic status of the host. Regardless of etiologic relation, however, the various disseminated granulomas frequently pose a difficult problem in differential diagnosis, and it is certain that they have been confused with sarcoidosis on more than one occasion.

Brucellosis. In view of its ability to involve practically every organ in the body, its frequently low-grade chronic course, its association with noncaseating granulomas and its world-wide distribution, brucellosis has been considered a possible cause. It is quite possible that typical sarcoid lesions may be produced, though the usual lesions tend to be much less distinct with proliferation of cells of the reticuloendothelial system, and occasionally suppuration.[264] Pulmonary involvement may resemble that of sarcoidosis,[265] iridocyclitis may occur, and the bones may be involved as well; the characteristic bone changes of sarcoidosis have not been described, however. In the cases in which specific skin or agglutination tests have been performed they have all been negative, and Harrell[42] found that guinea pigs injected with tissue from sarcoid patients remained negative to brucellergin. These arguments do not, of course, constitute proof but simply indicate that brucellosis in its usual form is not sarcoidosis. It is well known that failure to culture the organism or to obtain positive skin or agglutination tests does not necessarily rule out the disease,[264] whereas, on the other hand, occasional positive findings might indicate little more than their coexistence.

Syphilis. A number of cases reported as cutaneous sarcoidosis may have been due to syphilis.[266, 267] As noted above, however, the serologic reactions are negative in the large majority of sarcoid patients so that it seems unlikely that syphilis can be the responsible agent in any appreciable number of cases.

Mycoses. Some attempts have been made to implicate various yeasts and fungi as etiologic agents, usually on the basis of a similar pulmonary picture. Organisms such as aspergillus and

monilia have been found in the sputum of patients on occasion,[30] but these organisms are often saprophytic and do not necessarily possess etiologic significance. Cutaneous tests with blastomyces filtrates, monilia vaccine or coccidioidin, when done, have given negative or at best faintly positive results.[42, 47]

Histoplasmosis occurs as a disseminated disease capable of involving most of the organs of the body and is now known to be world-wide in distribution.[268] It may also produce granulomatous lesions in which organisms are rare or absent.[269] The much higher incidence of histoplasmosis in infants and young children, the high male-sex incidence in the adult, the common presence of mouth and gastrointestinal lesions, the rarity of eye lesions and the high susceptibility of most laboratory animals[268] are findings at considerable variance with those of sarcoidosis; as in tuberculosis and brucellosis, however, such data prove only that the usual form of histoplasmosis is not sarcoidosis.

Tornell[270] has pointed out the resemblance between the radiologic picture of the lung in sarcoidosis and that of "thresher's lung," a form of moniliasis, or possibly histoplasmosis, due to inhalation of burnt grain. This disease is acute, but he suggests that chronic exposure of susceptible persons to moldy dusts, as in cellars and attics, could produce a similar picture. Since the pulmonary picture of sarcoidosis is nonspecific, however, such arguments are unconvincing. The same thing may be said for such equally nonspecific manifestations as erythema nodosum, the occurrence of which in both sarcoidosis and coccidioidomycosis led Kerley[153] to suggest an etiologic relation.

Leishmaniasis. Sarcoid forms of leishmaniasis have been described,[271] and certain clinical features such as hepatosplenomegaly and hyperproteinemia are suggestive. This seems an unlikely cause in most cases, however. Careful searches have been made for the organism in some cases without success,[24] but in some known cases of leishmaniasis, organisms may be very rare and difficult to find.[272]

Virus diseases. The inability to identify organisms in the lesions of most cases has suggested a virus etiology to some authors. Attempts to implicate the virus of lymphogranuloma inguinale by means of the Frei test, at least, have usually been negative. The Kveim antigen, at first regarded as strong evidence for a virus etiology, has been shown to be nonspecific and highly thermostable.[206, 208] If a virus is indeed the cause of sarcoidosis, it has yet to be demonstrated.

Inorganic Agents

The resemblance of the pulmonary forms of sarcoidosis to some of the pneumoconioses has suggested that they are related. The clinical course of silicosis, as well as the absence of silica in abnormal amounts in the sarcoid lesions, seems to rule this out rather definitely. Sarcoidosis has been described in association with asbestosis on at least one occasion,[273] but the two types of lesions appeared distinct.

Beryllium. The chronic form of a pulmonary disease occurring in workers exposed to compounds of beryllium bears sufficient resemblance to sarcoidosis to have suggested their identity to some authors.[274] The pulmonary picture may, in its later stages at least, closely simulate the roentgenologic findings of sarcoidosis, and some patients have also exhibited hilar and peripheral adenopathy, enlarged liver and spleen, and skin lesions. Moderate elevations in serum globulin and calcium have been observed, and in 1 case an elevated blood calcium was associated with renal stone.[275] Tuberculin tests have also been negative in a number of cases.[276] On histologic examination, granulomatous lesions composed of epithelioid and giant cells have been found in the lungs, lymph nodes, liver and skin, and deep-staining, concentrically laminated inclusion bodies of the type described by Schaumann in sarcoidosis have also been seen.[72, 73]

Claims for identity of the two conditions, as with other suggested etiologic agents, stress individual similarities and ignore the clinical picture as a whole. Unlike the usual case of sarcoidosis, which tends to be asymptomatic or practically so, the so-called delayed chemical pneumonitis or pulmonary granulomatosis is characterized by severe dyspnea, anorexia, weight loss, gastrointestinal disturbances and often cough and cyanosis. The disease is frequently progressive to the point of incapacitation, and cor pulmonale with right-sided heart failure frequently supervenes. In 45 cases collected by Hardy,[276] at least 7 patients died, and only a few recoveries after prolonged illness have so far been reported. Bone lesions have not been seen. Even the roentgenographic picture of the lungs resembles sarcoidosis only in its later stages and, as such, is hardly pathognomonic, whereas the earlier "sand-storm" appearance has been considered by some to be entirely unique.[72, 277]

Histologic examination of the lungs of these patients reveals granulomatous lesions, but the general picture bears only a superficial resemblance to that of sarcoidosis. Similar granulomas have been seen in lymph nodes and other organs. Histologic lesions closely simulating those of sarcoidosis have been noted in the skin of 2 patients with the chronic pulmonary disease, and in 3 others who cut themselves on broken fluorescent lamps.[73] In most of these lesions, however, foci of necrosis of a type never seen in sarcoidosis have been present. The relatively limited exposure to beryllium compounds makes this an unlikely cause for any great number of sarcoid cases, particularly since sarcoidosis obviously antedates the wide-

spread industrial use of beryllium. Nevertheless, it is possible that a few cases, particularly some with marked pulmonary fibrosis, dyspnea and cor pulmonale, have been so caused. The long delay in onset following exposure — up to five years in some cases — and the occurrence of the disease in persons who have lived close to, but never worked in, factories using beryllium[276, 278] may account in part for failure to obtain a history of exposure in such patients.

Nonspecific Agents

Localized sarcoid lesions have been observed following a wide variety of nonspecific stimuli, including the introduction into the tissues of such substances as paraffin and various medicated oils,[279–281] morphine, iron and arsenic preparations,[282, 283] and glass and stone fragments.[75, 76] Similar lesions have been noted at the sites of previous operations[29] or after trauma without known introduction of foreign substances into the tissue.[76] In many of these cases the histologic descriptions are inadequate, and some of them may simply represent foreign-body reaction; a few, however, have been of characteristic sarcoid structure. The granulomas are of the subcutaneous type, infiltrating connective tissue and muscle, and have in the past been grouped with the subcutaneous sarcoids of the so-called Darier–Roussy type. Giant cells may be numerous, and often contain asteroid or refractile inclusions. An interesting feature in most of these cases has been the long latent period between the traumatic episode and the onset of the lesion — varying from months to many years; a few have recurred after incomplete excision. It is possible that some of the isolated sarcoid lesions in the intestinal tract and other areas, as well as the local skin lesions produced by beryllium compounds, belong in this category.

Since the other features of sarcoidosis have not been associated, there is no justification for such a diagnosis in these cases. The wide variety of agents that seem capable of inducing such reactions — and the agent producing disseminated sarcoidosis appears to be only one — suggests some common underlying mechanism in their formation. Phospholipids, either introduced into the body or freed nonspecifically at the site of reaction, may represent such a common factor,[42, 176, 284] though in at least one study such substances have failed to cause characteristic reactions in patients with sarcoidosis.[227] It is possible, too, that foreign material capable of inducing a local histiocytic or reticuloendothelial response in some cases provides a site for localization of the etiologic agent of sarcoidosis during periods of dissemination; such a phenomenon is suggested by the occurrence of positive Kveim reactions only in patients with active disease. Whatever the responsible agent, however, an altered state of reactability either constitutional or acquired — in effect, the *terrain sarcoidique* of the early French authors[285] — may well be a contributory factor in the genesis of the lesions.[4, 53, 286]

Allergy. Certain features of sarcoidosis, such as the so-called tuberculin anergy and the occasional occurrence of such allergic manifestations as eosinophilia and erythema nodosum, suggest that hypersensitivity plays a role in the disease. There is recent experimental evidence to indicate that granulomas of histiocytic and even epithelioid character are associated with anaphylactic response.[287] Teilum[83] has also postulated an allergic basis for the hyalinization of sarcoid lesions. According to this concept, such changes are related to the hyperglobulinemia, and have as their starting point a globulin precipitate, especially in the reticuloendothelial system; these precipitates are gradually transformed, either within or outside the granuloma, into a homogeneous substance resembling amyloid (paramyloidosis or hyalinosis). Similar changes are described in other disorders associated with hyperglobulinemia such as Letterer–Siwe's disease, lupus erythematosus and lymphogranuloma inguinale, and are interpreted as the result of persistent and repeated stimulation of immune mechanisms.

* * *

Progress in the understanding of sarcoidosis in recent years has largely been limited to clarification of the clinical picture and recognition of some of the pitfalls in diagnosis. It has been amply demonstrated that no single feature of the disease is sufficient for diagnosis, and many errors have been made through the too-frequent substitution of the part for the whole. The pulmonary roentgenographic picture may be simulated by erythema nodosum, the mycoses, beryllium granulomatosis and a host of other conditions, the bone lesions by leprosy, the histologic picture by many agents both specific and nonspecific.

Most of the features of the disease are consistent with those of a chronic infection having a special predilection for the tissues of the reticuloendothelial system. Even the electrophoretic patterns obtained in examination of the blood proteins have been similar to those seen in other chronic infections, and a differential diagnosis between sarcoidosis and other widely disseminated infections is often exceedingly difficult. It is these close resemblances, in fact, that have given rise to most of the etiologic theories. Clinical diagnosis is further complicated by the fact that the disease progresses and regresses irregularly, with various localizations becoming evident or disappearing without definite temporal relation, or even stabilizing for long periods. It may therefore be necessary to follow some suspects for a considerable time before characteristic localizations make their appearance and definite diagnosis is possible. Obviously, the

greater the number of such localizations, the more certain the diagnosis will be.

Considerable confusion has also resulted in the past from the assumption that the morphologic appearance of the lesion is pathognomonic. When typical, the sarcoid lesion is highly characteristic, but many cases show sufficient departure from the generally accepted norm to make histologic differentiation from miliary tuberculosis, brucellosis or other granulomatous disease practically impossible. So little is actually known of the genesis of these lesions, particularly their early phases, that the extent of permissible variation is still largely a matter of conjecture, and pathologists disagree considerably among themselves regarding the morphologic criteria for diagnosis.

Even granting the presence of a typical sarcoid lesion, this alone cannot be construed to constitute diagnostic proof. A wide variety of agents, of which the unknown cause of sarcoidosis appears to be only one, seem capable of inducing the characteristic granuloma, and it has become increasingly clear that a careful distinction must be made between the "sarcoid lesion" and the disease "sarcoidosis." The evidence provided by biopsy is essential, but constitutes only one link in the chain of evidence required in making a reliable diagnosis.

The Kveim test, which has been found to be positive in a fair percentage of patients with active sarcoidosis, seems to be a significant recent development. The test in its present form is not especially practical as a means of diagnosis, but it may well shed some much needed light on the question of pathogenesis. In particular, the nonspecific character of the Kveim antigen raises again the question of altered tissue reactability on the part of the host, a condition that may also account for the well known and puzzling tuberculin insensitivity of many patients. Preoccupation with tuberculin, unfortunately, has resulted in too little investigation of reactability to other substances, and it is possible that sarcoid patients tested in appropriate endemic areas might show a refractiveness to coccioidin, histoplasmin or lepromin of the same order as that to tuberculin. The sporadic tests so far performed with such substances have usually been negative but as a rule have been done in nonendemic areas. Any such group would, of course, require careful diagnostic screening since all these conditions can simulate sarcoidosis in one way or another.

The etiologic issue is still far from solution and has made little or no progress in more than twenty years. The tubercle bacillus and some unknown agent, perhaps a virus, remain the most favored possibilities, but no real proof has yet been offered. An organism of the brucella group may also be involved. Whether further careful bacteriologic or viral studies, or study of inoculated animals for longer periods, will shed more light on this issue remains to be seen, but this approach does not seem to be particularly hopeful at present.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34461

PRESENTATION OF CASE

First admission. A five-year-old girl was admitted to the hospital with a small nonpainful lump in the right axilla, which had been present for a year and had increased in size over this period and spread up under the clavicle. Immediately before admission to this hospital the child had been taken to a clinic because of tonsillitis. Chest x-ray films were reported at this time to show an "intrathoracic tumor." An exploratory operation showed "a grayish, ropy, polycystic mass." The outer portion was attached to the fibers of the pectoralis major, and the inner portion extended deep to the pectoralis and disappeared under the clavicle. Following this the patient was admitted to this hospital.

Physical examination showed a moderately well nourished, underdeveloped child. The right pupil was smaller than the left and eccentrically placed. There were numerous large, pigmented areas over the entire body, with the exception of the lower extremities. The superficial veins of the right upper chest were prominent, and the right arm appeared cyanotic. Masses were present immediately beneath the skin in the right axilla and in the right supraclavicular fossa. The right upper chest was dull anteriorly and posteriorly, and the breath sounds were decreased. At the extreme apex there was an area of bronchial breathing. The pulse at the left wrist was greater than that on the right. The only positive neurologic finding was weakness of the right hand. Urine and blood examinations were negative. A chest x-ray examination was reported as follows: "Findings are those of a large mass in the upper mediastinum rising posteriorly, probably lobulated, a smaller lobe being on the left side, with soft-tissue masses in the right supraclavicular and right axillary region." An operation was performed through a paravertebral approach, and portions of the second, third and fourth ribs on the right were resected. The tumor was found to be a neurofibroma of the invasive type, but a large portion was removed and the brachial plexus was freed. The patient did well postoperatively and was discharged on the twenty-fourth hospital day.

Final admission (twelve years later). In spite of the progressive character of the disease, resulting in increasing skeletal deformity, exertional dyspnea and also apparent hypogonadism, the patient completed school and was able to accept summer employment. In this interval she received some radiation treatment. One year before admission while being followed at another clinic the tumor in the right side of the neck began painlessly to increase in size. Four weeks before admission her voice weakened and became hoarse. Two weeks before admission she suddenly awakened with extreme shortness of breath. This was not associated with pain or cough or sputum, and since then she had slept in a semi-squatting position, with her legs tucked under her. Following this she noted swelling around the eyes, face and neck, most marked in the morning, and most severe on the left side. Difficulty in swallowing large mouthfuls was noted, and severe supraorbital headaches, worse at night than

in the morning. There was no history of chills, fever or weight loss.

On physical examination the patient was poorly developed, orthopneic and markedly kyphoscoliotic. There were small plaques of pigmentation over the arms and trunk, with a marked area extending from the anterior axillary line at the level of the nipple extending along the medial surface of the right arm and involving the axilla. A firm, smooth, fixed mass, 15 cm. in its longest diameter, was present in the right supraclavicular area. There were small, shotty nodules in the right axilla and beneath the skin along the posterior axillary line. The superficial veins of the neck on both sides were distended, and the veins of the right hand failed to empty on full elevation. The blood pressure was 110 systolic, 80 diastolic, in both arms. The left border of the heart reached the left anterior axillary line. The temperature, pulse and respirations were normal. There was extreme weakness and areflexia in the right upper extremity. There was marked sexual underdevelopment. An electrocardiogram was normal. An x-ray examination of the chest was reported as follows: "There is marked, severe kyphoscoliosis of the dorsal lumbar spine so that the heart is on the right side of the thorax. Size and shape of the heart cannot be determined because of the severe deformity. There has been partial resection of the right upper ribs. A soft-tissue tumor is present over the dorsum of the right side of the chest." Urinalysis was negative. Blood examination showed a hemoglobin of 12.5 gm., and a white-cell count of 11,000, with a normal differential.

While in the hospital she developed rather severe precordial pain, which was pounding in character and located over the apex. There was very little that could be done for this girl except to supply sedation. On the eighth hospital day while she was sleeping at night it was noted by the nurse that respirations had stopped but the pulse was still present. Resuscitation measures were of no avail.

Differential Diagnosis

Dr. Earle M. Chapman: May we see the x-ray films?

Dr. Joseph Hanelin: There is an extremely severe spinal deformity, rather marked kyphoscoliosis or perhaps mostly scoliosis. The heart is just visible within the right thorax. There have been resections of the right upper ribs, and some rib regeneration has taken place. There is no obvious explanation for the scoliosis in the way of any structural or bony abnormality. There is evidence of a soft-tissue tumor in the right side of the thorax. There is a mass in the region of the right axilla. In the lateral view of the chest, which includes a large part of the patient, the abdomen appears to be somewhat protuberant. There is soft-tissue density present, with a lobulated appearance, which is observed to extend through the dorsal aspect of the thoracic wall. I cannot be certain that this lesion is within the thoracic cavity, although this is a general situation and cannot be interpreted particularly without stereoscopic films because of the marked deformity.

Dr. Chapman: May I ask if you see any area in the bony structure that suggests metastatic or destructive lesions?

Dr. Hanelin: No, I do not.

Dr. Chapman: Do you see any lesions in the vertebral column?

Dr. Hanelin: No, I see no lesions at all in the vertebras.

Dr. Chapman: Is this a right dorsal kyphoscoliosis?

Dr. Hanelin: It is to the left.

Dr. Joseph Aub: May I add some information that Dr. Chapman ought to have? The patient had extreme cyanosis of the face and really had an enormous amount of dyspnea, which I do not think the record makes clear.

Dr. Chapman: From the evidence at hand it seems to me that this girl suffered from two diseases, either one of which alone would have brought about her death, and certainly both together have done so. The first is that she had multiple neurofibromatosis of the invasive type, diagnosed histologically here in this hospital twelve years before death. Then on top of these tumors that no doubt were multiple, she had an increasing deformity of the chest, which we are told was a left kyphoscoliosis compressing the lungs and the soft tissues within the chest to the point where the vital capacity was greatly diminished. Life was a battle. She was struggling to live in the face of great diminution of the pulmonary reserve, and she must have had what I once called pulmonocardiac failure.[1] The interference with breathing, the cyanosis and the description here indicate that there was also occlusion of venous return in the superior mediastinal region. One would think that the tumor produced a superior mediastinal syndrome more marked on the right than on the left according to the description. Beyond that I think any remarks are purely speculative as to what might be found at autopsy. I think, however, the description of the hypogonadism and the statement of the sexual underdevelopment warrant a few remarks. I would like to have information, for instance, whether or not the 17-ketosteroids were determined. I judge they were not done.

Dr. Jacob Lerman: No.

Dr. Chapman: There are perhaps androgen-producing tumors of the adrenal glands that could produce some of the signs present. One wonders if neurofibroma was present in the adrenal area or if one or both of the adrenal glands were involved in this type of tumor. One wonders if she had some other type of hormonal tumor of the adrenal cortex, producing the so-called adreno-

genital syndrome, which comes on after puberty. At the age of seventeen her changes could go with a disordered pituitary function, and the signs are not classic of a type of adrenal tumor that comes on after puberty or before puberty. I see no way to include or exclude these possibilities. We have no index from the laboratory procedures recorded. I think this girl's death was due to progressive failure of the lungs, and it got to the point finally where she did not have enough respiratory exchange to survive.

Did she have some disease in the coronary arteries? You will recall that later in the history it says that she suffered from precordial pain, which was pounding in character and located over the apex despite the previously normal electrocardiogram. I assume that the electrocardiogram was taken before that pain, although the record is not clear on that point. One wonders about coronary occlusion with myocardial infarction as a terminal episode. This form of accident in kyphoscoliotics is unusual; in fact, it is rare. The patients usually die, and at autopsy the heart is found to be hypertrophied, chiefly in the right ventricle and even in the right auricle, and yet seldom do they have signs of coronary-artery disease and likewise seldom, if ever, hypertension, although a few have been described in which the hypertension is present in addition to a pulmonocardiac syndrome.

I can add very little to this discussion. Perhaps you can, Dr. Aub. You saw her on the wards, and I think I have covered the possibilities that I can see in this case.

Dr. Chester M. Jones: Probably she had been more or less anoxic and increasingly so for quite a few years. That condition was present during puberty. Might not that in itself have been sufficient to account for the sexual immaturity and incomplete growth?

Dr. Chapman: I do not know how one could tell, but that is a fair statement. In general, kyphoscoliotic patients who begin the deformity early in life continue to be immature, without great sexual development. It would be a possibility just as a matter of general nutrition and general metabolic processes being lowered, and the hypogonadism being a part of it. On the other hand, we have seen these patients come through life and bear children and seem quite normal sexually, or they have no such stigmas of endocrine dysfunction as this patient had.

Dr. Tracy B. Mallory: Have you anything to add, Dr. Aub?

Dr. Aub: No, I agree with Dr. Chapman. We thought that the hypogonadism might be due to prolonged anoxia and cyanosis, but the sexual immaturity we blamed on the pituitary body; otherwise we reasoned the way Dr. Chapman did.

Dr. Lerman: When she came on the ward she was a malnourished, underdeveloped, pathetic creature, very orthopneic and dyspneic. The picture of kyphoscoliosis was complicated by the neurofibromatosis, which involved the superior mediastinum and the right chest, and produced superior mediastinal syndrome — marked distention of the neck veins, and facial edema. It was our impression that the underdevelopment of the sex activity was related to the combination of anoxia and malnutrition.

Dr. Mallory: Have you anything to add from the surgical point of view, Dr. Scannell?

Dr. J. Gordon Scannell: She was seen in the Thoracic Clinic with the question of possible superior mediastinal syndrome. Obviously nothing could be done.

Dr. Lerman: It was our impression that the kyphoscoliosis developed probably from progressive paralysis of the intercostal nerve as it grew. The kyphoscoliosis had been present for many years.

Clinical Diagnoses

Pulmonocardiac failure.
Neurofibromatosis.
Superior mediastinal syndrome.

Dr. Chapman's Diagnoses

Multiple neurofibromatosis, invasive type.
Kyphoscoliosis, left-sided.
Pulmonocardiac failure.
Androgen-producing tumor of adrenal gland?

Anatomical Diagnoses

Neurofibrosarcoma, with invasion of right innominate vein and superior vena cava.
Superior-vena-cava obstruction.
Left dorsal scoliosis.
Pulmonary atelectasis.
Hypogenitalism.
Hyperplasia of adrenal glands.

Pathological Discussion

Dr. Mallory: At post-mortem examination a very large tumor was found in the axilla and upper mediastinum on the right side. It was very difficult in the midst of the multiple lobules of the tumor to identify normal structures. We were unable to identify the vagus or the phrenic nerves. The carotid arteries passed through the tumor and were apparently uninvolved except perhaps by pressure. The internal jugular vein could not be identified, and the innominate vein appeared to be completely occluded by a mass of tumor tissue, which dangled down the superior vena cava to within about a centimeter of its mouth into the auricle. The brachial plexus was unrecognizable in the midst of the tumor, and there was enough tumor within the thoracic cage to have caused extensive collapse of the right lung. The heart was quite small, as were

all the other organs, and there was no evidence of right-sided heart hypertrophy or dilatation of the right auricle. We found no passive congestion of the liver, spleen or kidneys, such as one might expect to find with kyphoscoliotic heart disease. I do not think we can give a dogmatic opinion in this regard. To what extent this tumor of the vena cava may have been responsible for the cardiac symptoms, I do not know. It came so close to the auricle that, with slight change in posture, it is not inconceivable that it could have dipped into the auricle at times. It was quite evident that death was sudden because the liver showed the marked glycogenation that one ordinarily sees in patients who die suddenly with an acute coronary attack or pulmonary embolism. The spine showed no disease of the bone or intervertebral disks, and the scoliosis, I am sure, was functional rather than structural. The uterus was quite small and almost infantile in dimensions. The ovaries were small and showed only slight activity. There were a few small ova and graafian follicles but almost no scars of corpora albicantia. The pituitary body was small and grossly normal. The adrenal glands, in contrast, were quite large, probably slightly larger than normal, but otherwise not remarkable. From their histologic appearance I would expect excess rather than decrease of the adrenal function.

DR. AUB: How about the pituitary body?

DR. MALLORY: It appeared small but otherwise normal.

DR. CHAPMAN: I am intrigued by what you said about the size of the adrenal glands in proportion to the other endocrine glands, and you are not able to estimate of course the degree of function from observation histologically.

DR. MALLORY: No.

DR. CHAPMAN: It is of considerable interest that Cahill[2] in a recent article reports that the most frequent cause of changes from excess androgen is bilateral adrenal hypertrophy and that "with the exception of survival time there is often no difference between the symptoms of bilateral adrenal hypertrophy and unilateral tumor."

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CASE 34462

PRESENTATION OF CASE

A fifty-seven-year-old woman entered the hospital complaining of attacks of heartburn, distention, indigestion and abdominal cramps, which had been present for a number of years.

In the four-year period prior to admission these symptoms had all increased in severity. In addition she recently had palpitation, regurgitation of food and a sensation of food sticking in her chest. Walking relieved the symptoms. The discomfort and heartburn always followed meals. X-ray studies done elsewhere four years previously revealed a diaphragmatic hernia. In the three or four months prior to admission she had felt much weaker than usual and had black stools. The hemoglobin had repeatedly been found to be low. There was one episode when she became pale and went into shock and the hemoglobin dropped rapidly. This was treated by transfusion. There had been no weight loss.

On physical examination the heart was not enlarged. The chest and abdomen were normal.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 65 diastolic.

Laboratory examination revealed a normal urine and a guaiac-positive stool. The hemoglobin was 11.8 gm., and the white-cell count 13,000, with a normal differential. There was moderate variation in size of the red cells; platelets appeared slightly increased; there was no achromia. A chest x-ray film and barium enema were reported negative. A gastric series was done just prior to admission here. These outside films were interpreted here, without a fluoroscopy being done at this hospital, as showing a hiatus hernia and a smooth narrowing in the distal esophagus over a distance of 3 cm., with dilatation proximal to this point.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. GORDON SCANNELL: The problem boils down to that of a fifty-seven-year-old woman who had symptoms pointing to the esophagus. They were symptoms of irritation, obstruction and bleeding. Looking first at the historical evidence, I would consider the following to be of significance. First of all, there was increase in symptoms over a relatively short period, four years. "Recently," which is not defined, there were palpitation, regurgitation and esophageal obstruction. So we wonder if she did not have the change in gastrointestinal symptoms, a change that raises the question of new growth in the gastrointestinal tract or any system of the body. She apparently had heartburn for a good many years, as well as distention and abdominal cramps. The latter are hard to explain on the same basis as heartburn, a symptom of esophageal irritation. Another bit of historical evidence is that four years before admission a diagnosis of diaphragmatic hernia was made, which apparently did not raise the suspicion of cancer. We assume, therefore, that some change had taken place in the x-ray picture. Furthermore, there was significant blood loss through the gastro-

intestinal tract for three or four months, with one massive hemorrhage.

Physical examination helps me very little, and the laboratory studies add little, at least to my interpretation of the problem.

We might look at the x-ray films. The barium enema was done to explain the symptoms of abdominal cramps and distention and is reported as negative. The chest films were reported negative also, although on looking at them I wondered if she had dilatation of the great vessels.

DR. JAMES J. MCCORT: It is difficult to say much about the esophageal lesion on the single outside film available and without being able to fluoroscope the patient. On the film available we find that the proximal esophagus is dilated. This terminates in a narrowed area 3 cm. in length. Below this is a fairly large hiatus hernia within which the rugal folds have the appearance of gastric mucosa. There is a suggestion of a shelf defect on the upper posterior margin of the narrowed zone in the lower third of the esophagus. The edge of the narrowed area is slightly irregular; it may be slightly nodular, but this is hard to tell, since there may be mucous flecks mixed with the barium. The lower margin does not show a shelf defect. There is possibly a soft-tissue tumor of the narrowed segment, but this cannot definitely be determined on the one film available. The remainder of the stomach and the duodenum do not show any abnormality.

DR. SCANNELL: I wondered about the area that you agree is suggestive of a shelf. I am interested that you agreed that the duodenum, without palpation I realize, was normal. The presence of a duodenal ulcer might be an additional red herring.

DR. MCCORT: We do not have sufficient films to determine whether it is a persistent shelf defect. The lungs are clear. The heart is not enlarged. There is slight tortuosity of the aorta.

DR. ALLAN M. BUTLER: Why could they not do fluoroscopic studies?

DR. SCANNELL: These are outside films, and that is all the evidence we have.

DR. RICHARD H. SWEET: The patient had an adequate study before entry to this hospital, and we thought it would be redundant to repeat it here.

DR. BUTLER: That is a very satisfactory explanation.

DR. SCANNELL: In this case of course we know that she had a diaphragmatic hernia, and the question is whether or not that would explain all her symptoms. One might suppose that it was incarcerated, and incarceration is certainly associated with bleeding and it can explain the esophageal obstruction. One can assume that it was the diagnosis and sufficient indication to warrant surgery on the basis of bleeding and obstruction, which are disabling. However, we are suspicious because of the change in character of the symptoms and because of the x-ray picture, which on the films available, is not that of an entirely smooth narrowing of the lower end of the esophagus. It is certainly true that we do not have to make a diagnosis of cancer because hiatus hernia is frequently associated with a good deal of esophagitis and benign stricture of the lower end of the esophagus. I do not know the exact number of cases, but the latter are frequently associated with infradiaphragmatic disease in the nature of a duodenal ulcer, or possibly disease of the biliary tract and, therefore, it is a tenable diagnosis in this patient. A diagnosis of benign disease would be all right if we could agree that it was smooth narrowing and even better if we could demonstrate a small, benign-appearing ulcer. But in any event we would have to visualize this area to satisfy ourselves whether or not carcinoma were present. I think that the question of a dilated and tortuous aorta encroaching on the hiatus is a theoretical possibility but most inadequate to explain the symptoms. An unusual lesion in this region might be lymphoma, which I assume may occur here, although I have never seen one, and specific or nonspecific inflammation in the nature of syphilis; but there is no evidence to make that diagnosis.

Therefore, I come back to whether or not this patient had a carcinoma in the esophageal hiatus hernia, and I am inclined to think that she had, in spite of the fact that she had a little dilatation of the esophagus, which she may have had with her hiatus hernia over the years and which, therefore, certainly does not rule out carcinoma. I am basing it chiefly on the fact that she had changes in her symptoms in a lesion that she had had for many years — also, on the x-ray picture, which first of all, I gather, is suggestive of a soft-tissue mass, although that could be omentum or something in the hiatus hernia, and secondly, is suggestive of an irregular narrowing of the lower end of the esophagus. Therefore, on the eighth hospital day this was either visualized through an esophagoscope or, if the patient was a good risk, exploration carried out for sufficient indications even disregarding the suspicion of cancer. But I think we are justified in making a diagnosis of probable carcinoma of the lower end of the esophagus.

DR. TRACY B. MALLORY: Dr. Sweet, will you tell us your clinical impression?

DR. SWEET: There are several very interesting aspects to this case from the standpoint of the history as well as the findings at operation, one of which is that in my experience with carcinoma of the esophagus massive hemorrhages are exceedingly rare. They occur in carcinoma of the stomach, but I do not recall any from carcinoma of the esophagus. I have encountered one case of lymphoma of the esophagus. Although lymphoma in other parts of the gastrointestinal tract may cause massive bleeding, that particular patient had none.

Another thing about the history that Dr. Scannell did not have the benefit of is that she had improved

considerably in the past two months as manifested by the facts that she had stopped bleeding and she had less pain. The symptoms were not progressive the way they are almost invariably in carcinoma. In quite a large series of cases of carcinoma of the lower end of the esophagus and cardia that we have operated on here, I do not recall the exact figures, but approximately 13 per cent arose in this particular type of case in which there was a short-esophagus type of hiatus hernia in which there probably had been, or might have been, considerable esophagitis, ulceration and fibrotic stricture. We were, therefore, prepared in this patient to find either a carcinoma or an esophagitis.

Clinical Diagnoses

Peptic ulcer of esophagus in hiatus hernia.
Chronic lymphadenitis.

Dr. Scannell's Diagnoses

Carcinoma of esophagus.
Diaphragmatic hernia.

Anatomical Diagnoses

Peptic ulcer of esophagus.
Diaphragmatic hernia.

Pathological Discussion

Dr. Sweet: At operation the lesion was found to be quite characteristic of esophagitis. The periesophageal tissues in the mediastinum, as they usually are in that condition, were very much thickened. Dissection of the esophagus was difficult, — it is always more difficult in that lesion than it is in carcinoma, — and there was evidence of reaction all the way up the mediastinum as far as I pursued the esophagus. The area where one can see narrowing on the x-ray film was very firm but not so firm as carcinoma would be. It felt rather rubbery. The herniated portion of the stomach was not particularly unusual except that it was adherent, and the majority of these hernias are not unless there is some interference with the blood supply from an incarceration. I think she had had a lot of mediastinitis. After the esophagus and stomach had been dissected free from the surrounding tissues it was possible to reduce the stomach below the diaphragm. In other words, this case was characteristic of the majority of cases of hiatus hernia. The shortness of the esophagus is more apparent than real. A true congenitally short esophagus is very unusual, but it does occur. Because of the lesion in the lower end of the esophagus, I chose to do a resection.

Dr. Butler: Would a fluoroscopic examination have helped to make this diagnosis?

Dr. Sweet: It was done at the time the films were made, but I do not believe it helped in this case.

Dr. Mallory: The resected segment consisted of the lower 3 or 4 cm. of esophagus and approximately equal portions of the cardia of the stomach. Just above the junction of the esophagus and stomach was an area of shallow ulceration from which the mucosa was completely denuded. Histologic examination of that area showed a fibrinoid membrane of the type that we characteristically see in active peptic ulcer. Peptic ulcers of the lower end of the esophagus are unusual but not extremely rare lesions. I believe that was the etiology of the ulcer in this case.

Dr. Sweet: It looked to me on examining the gross specimen as we resected it as if the ulcer was completely annular. I could not see any normal mucosa whatever.

Dr. Mallory: There was no mucosa of any significance.

Dr. Sweet: Do you think that these peptic ulcers in the lower end of the esophagus usually occur in the extension of gastric mucosa that we so often see in the lower end, or do you think they frequently occur in the mucosa, which is characteristic of the esophagus itself?

Dr. Mallory: Judging from the literature usually it is possible to show that there was extension of the gastric mucosa into the esophagus in the majority of these cases. This is not clearly evident here because of the complete denudation of the mucosa.

Dr. Sweet: I have a distinct impression that the majority of these ulcers occur in upward extensions of the gastric mucosa, although they are actually in the esophagus.

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CONCERNING THE DOCTOR DRAFT

There is good reason to believe that early in 1949 Congress will debate an amendment of the Selective Service Act to remedy the shortage of physicians in the newly expanded armed forces. What the public reaction will be, both medical and lay, remains to be seen, but already cries of distress and charges of discriminatory legislation are being faintly heard in medical circles. Although it is too soon to pass judgment on legislation not yet born, it may be permissible to indulge in a little basic thinking on some of the issues underlying any draft of doctors.

For example, it is well to bear in mind Congress's purpose in undertaking this postwar expansion. Primarily it is to put teeth into its belated efforts to prevent World War III, and failing that, to give the kind of civilization in which we all believe a reasonable chance for survival in what would amount to a war of extermination — at least of ideologies. These would appear to be objectives to which only our enemies could take reasonable exception, but, as the country has already learned to its cost, no objectives, however greatly desired, are attained by wishful thinking.

The magnitude of the stake must never be forgotten. By now it should be clear to everyone over twelve years old that if another world war is not prevented there will be no question of seizing grandpa's musket from over the fireplace and hastening to Concord or Lexington. Nor will it be simply a matter of providing medical officers for the armed forces, by draft or otherwise. Every man, woman and child will be involved, and there will be no time for claiming constitutional rights, because the very existence of constitutional government will be in the balance.

But we have not come to such a pass yet, and, please God, with wisdom and resolution we shall not come to it. Congress's contemplated action will concern chiefly doctors who were trained under ASTP and V-12 at Government expense but were unable to complete their term of active duty owing to the sudden (and as it now seems, premature) demobilization of the country's military force. If they should be required to complete their contract by a few months of peace-time service, it would seem too reasonable a sacrifice to be fairly resented.

While one indulges in basic thinking, it may be well also to contemplate the alternative method of enrollment for service in time of public need. The volunteer system, if system it may be called, may have the advantage of avoiding compulsion, but it has also certain glaring faults. It is unfair. It rewards the shirker, the parasite and the self-seeker while it penalizes the willing, the conscientious and the ready. Most citizens are glad to do their share of the dirty work so long as everyone else is doing his, but they dislike being played for suckers. Its second obvious defect is inefficiency. There can be no assurance that the person who volunteers is qualified, or even needed, for the job. Finally, the volunteer system has been and still

is being tried almost to the point of bribery, but without success.

It need not be concluded on that account that the failure to meet military quotas by voluntary enrollment means a tendency on the part of the profession to shirk its duty. Rather, it may be considered a reflection of the ordinary man's desire for fair play and the thoughtful man's appreciation of the importance of meeting his country's vital undertakings with an equal efficiency of action. It is earnestly believed that any future legislation that is fair, efficient and necessary will be approved by the medical profession regardless of the personal sacrifices it may demand of individual physicians.

PENICILLIN DOSAGE AND BLOOD LEVELS

The problem of dosage of penicillin at present is considerably different from what it was when the antibiotic first became available and it was both scarce and expensive. The general tendency is to use amounts that are far greater than those that could be deemed necessary in most infections by any consideration of the sensitivity of the causative organisms and by the blood levels attainable. The purified crystalline preparations now available are relatively nonirritating, so that aqueous solutions in sterile water or physiologic saline solution in concentrations up to more than 100,000 units per cubic centimeter can be given with a minimum of discomfort. Doses of 100,000 units or more are often used every two or three hours in the treatment of acute bacterial infections due to such organisms as the pneumococcus and the hemolytic streptococcus, which in most cases are sensitive to between 0.01 and 0.08 units per cubic centimeter.

Considerable early experience has shown that doses of 10,000 to 15,000 units every three or four hours are quite adequate for most of these cases. Furthermore, recent observations by a number of experienced workers and some of the earlier results have indicated that cures may be effected in cases of lobar pneumonia even when intervals of eight to twelve hours are permitted each day during which no injections are given. This is true in spite of the fact that penicillin activity cannot be demonstrated in the blood during the greater part of this interval.

Eagle[1] very ably discussed the significance of the penicillin blood levels at last year's meeting of the American College of Physicians. A brief summary of his speculations, which are based on a considerable amount of experimental evidence, should be of interest.

Eagle argues that the penicillin blood level is of significance only so far as it provides a rough measure of the concentration in the tissues at the site of the infection. The curve of the tissue levels after an injection of penicillin is important and may be expressed in terms of three time periods: the length of time for which penicillin is present at maximally effective concentrations that kill the organism at the fastest possible rate; the time for which penicillin is present at somewhat lower concentrations that are more slowly bactericidal; and the period after the penicillin has fallen to concentrations lower than those that kill bacteria in vitro but during which the organisms continue to die in the body at a rate faster than they multiply. This continuing death of organisms may be due to penicillin that persists in the tissues longer than it does in the blood, or the organisms may be killed by lower concentrations of penicillin in the body than they are in the test tube, owing perhaps to the participation of the body's defenses, or the organisms that have been exposed to penicillin may recover from its deleterious effects slowly and during a temporary period of retarded multiplication they may be disposed of by the defense mechanisms of the host. Whichever the cause may be, the period of gradually disappearing penicillin activity provides a margin of safety in that the blood and tissue penicillin levels may be permitted to fall below those that are significantly bactericidal in the test tube without affecting the outcome of treatment.

Large injections of penicillin are more effective than small injections, according to Eagle, not because they provide higher absolute levels of penicillin, but because they provide the effective concentrations for longer periods of time. More organisms are thus killed by each injection, and fewer survive to remultiply in the interval between injections. That interval may then be prolonged because with fewer surviving organisms less harm is done by a penicillin-free interval during which the organisms multiply. In general, therefore, it should

not be necessary to maintain the blood and tissue concentrations continuously at effective levels to attain a cure. Nevertheless, the most rapidly effective method of treatment, except in certain special circumstances, is still to repeat injections at such frequency as to maintain the tissue levels continuously in excess of the concentration that kills organisms at the maximal possible rate.

If Eagle's thesis is correct, the therapeutic activity of a given dose of penicillin depends primarily on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration in addition to the time required for the organism to recover from the drug and effectively resume multiplication. The enormous differences observed in the curative penicillin doses when either the number of injections or the interval between them is varied should then rest primarily on the total period of effective penicillin action. Conversely, different schedules of treatment that have the same biologic effects should provide effective levels for the same total period, irrespective of the total curative dose used.

Eagle has carried out many experiments in support of his contention. In the meantime, a certain amount of evidence had accumulated from other sources to indicate that frequent doses may be unnecessary. Thus, it has been shown that the 100 per cent curative daily dose of penicillin for pneumococcal infections of mice is the same whether two injections are given daily every twelve hours or eight injections every three hours.[2] In streptococcal infections in mice, the daily penicillin dosage given in a series of small equally spaced amounts was no more effective than equivalent amounts given in one or two doses a day.[3]

In the treatment of human cases of pneumonia, likewise, small doses at rather long intervals were first used successfully in the earliest clinical trials by Tillett et al.[4] More recently, doses of 300,000 units in aqueous solution given every twelve to twenty-four hours have been used successfully at the New York Hospital,[5] and similar dosage schedules employing large individual doses of aqueous penicillin one to three times a day are being practiced in a number of other clinics. In one of the large Boston hospitals a dosage of 100,000 units of aqueous penicillin every eight hours has been used for the treatment of most cases of pneumococcal and streptococcal infections for some time. In a series of cases of pneumococcal pneumonia recently reported by Price,[6] patients who received large doses of penicillin in aqueous solution twice daily responded as favorably as those who received the same total dosage at more frequent intervals. Of course, larger and more frequent doses are required for infections with more resistant organisms, such as many staphylococcal infections and subacute bacterial endocarditis. No doubt the patient will appreciate the longer intervals between the injections, which should also serve to reduce somewhat the burden on the nursing staffs.

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PUBLIC HEALTH IN INDIA

The Government of India Information Services in an Independence Anniversary Review points out some of the difficulties India is encountering in her efforts to improve public health. The report also indicates the determination with which the new Government is attacking its problems, and augurs well for an eventual successful solution of them.

Many of the problems, of course, are of an emergency nature and are concerned with the unsettled condition of the country and the mass movements of population between India and Pakistan. Huge refugee camps have required medical relief, the camp at Kurukshetra having at one time accommodated 300,000 refugees under canvas, for whom a thousand-bed hospital was established by the director-general of Health Services. Campaigns of inoculation and vaccination against cholera, smallpox and tuberculosis have been organized, nearly 40,000 BCG vaccinations having been done up to the end of June, 1948. Periodic delousing operations have been carried out in this city of tents,

and fly and mosquito control measures have been developed and enforced.

In addition plans for more permanent programs are being initiated. Health legislation has been passed and the reorganization of Delhi hospitals has been outlined. Steps are being taken for the establishment of health centers in Delhi Province and elsewhere. A program is under way for the improvement of medical schools and research institutes and for the development of postgraduate training.

The Health Ministry has moreover found the time and personnel to participate in various international conferences that have been held during the year. Delegations were sent to the International Cancer Research Conference in St. Louis in 1947, to the International Leprosy Congress in Cuba, to the International Congress on Tropical Medicine and Malaria in Washington last May, to the BCG Congress in Paris and to the first World Health Assembly at Geneva.

A tuberculosis institute is to be established in connection with the University of Delhi, and increased Government grants have been provided for the Tuberculosis Association of India. The activities of the Malaria Institute of India have resulted in further reduction in the incidence of malaria in Delhi.

Mother India, with her new-found freedom, is in fact fast becoming a modern mother. She has taken on the new look and has every intention of joining the other forward-looking mothers of the world.

THE JAPANESE MEDICAL JOURNAL

We welcome into the field of medical journalism *The Japanese Medical Journal*, of which the first two issues have come to hand, those of February and April, 1948. *The Japanese Medical Journal*, in English, is the official publication of the National Institute of Health of Japan, under the managing editorship of Hidetake Yaoi. Its contents, selected from papers submitted by all research institutions throughout Japan, may be considered, as the editor states, to be representative of the type of work being carried out in that country.

This journal, in a medical sense, is the first fruit of a reconstituted Japan. May it be representative of a new life and a new outlook; a step toward membership in a new society of nations that will look only in the direction of peace and the betterment of mankind!

ROBERT N. NYE MEMORIAL FUND

The Nye Memorial Fund has recently been increased by an additional gift of $1000 from a previous donor.

MASSACHUSETTS MEDICAL SOCIETY

VETERANS ADMINISTRATION FEE GUIDES

In order to give the subject of fee guidance schedules widespread publicity, the chief medical director of the Veterans Administration has requested that the following letter be reprinted in the various state journals. It first appeared in the *Journal of the American Medical Association*, May 22, 1948.

H. Quimby Gallupe, *Secretary*

Dr. Morris Fishbein
Editor, the *Journal of the American Medical Association*
535 North Dearborn Street
Chicago, Illinois

Dear Dr. Fishbein:

It has come to my attention that considerable misunderstanding has developed throughout the medical profession concerning the establishment of fees for medical services to be paid private physicians participating in the so-called "Home Town Medical Care Program for Veterans." It has been contended that the Veterans Administration has arbitrarily established a Fee Schedule which represents the maximum amount which may be paid for any given service and which is, in effect, a National Fee Schedule. It has also been contended that the various State Medical Societies and other interested groups were not consulted when this Fee Schedule was adopted.

In order to clear up any misunderstanding regarding this matter, it is desired to emphasize that my predecessor, Dr. Paul R. Hawley, had no intention at any time of establishing a National Schedule of Fees, nor do I contemplate doing so. However, the Fee Schedules originally submitted by the various State Medical Societies, when the "Home Town Medical Care Program" was inaugurated, varied so widely in format, terminology, and fees for similar or identical services, that it was deemed advisable to establish a uniform Fee Schedule Format and to set up tentative fees which could be used as a guide by the various State Medical Societies when submitting their proposals for the furnishing of medical care to veterans.

This uniform Fee Schedule Format was formulated by the Professional Group of National Consultants to the Chief Medical Director. This Group, representing the various specialties in medicine and surgery, is composed of eminent physicians from all parts of the country. Tentative fees were set up in the format after a careful analysis of Pre-Paid Medical Care Plan, Workmen's Compensation and Insurance Fee Schedules, and also the Fee Schedules in effect in the various States having agreements with the Veterans Administration. As was to be expected, considerable variation occurred in the Fee Schedules reviewed. The Professional Group of National Consultants made every effort to arrive at fees that were considered to be within reasonable limits and which would, as nearly as possible, allow a uniform provisional fee schedule for use as a guide in facilitating and expediting the preparation of agreements between State Medical Societies and the Veterans Administration.

Further attempt was made to provide for elasticity in the charges for certain operations or other services which seemed to evoke more than average contention by listing the minimum and maximum amounts considered equitable. These items bear the notation "AA," which indicates that the fee for the given service is to be determined by arbitration and agreement between the Veterans Administration and the Medical Society concerned.

May I reiterate that the Veterans Administration Fee Schedule Format is in no sense to be construed as an arbitrary or National Fee Schedule. Furthermore, it is subject to periodic review and such modification as conditions may indicate.

If it meets with your approval, I would appreciate it very much if you could possibly arrange to publish this as an open-letter in the *Journal of the American Medical Association*. I should like this to reach all the physicians throughout the country, and I know of no better way to do it than through the *Journal*.

PAUL B. MAGNUSON, *Chief Medical Director*

Veterans Administration
Washington 25, D. C.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RICE DIET

The rice diet is at present in common use for the relief of hypertensive states. Patients upon diets prescribed for such therapeutic purposes not infrequently develop nutritional deficiencies as a result.

The Massachusetts Department of Public Health, therefore, desires to call attention to deficiencies of the unsupplemented rice diet. The rice diet frequently prescribed for hypertension may bring about nutritional deficiencies in certain patients with previously poor nutritional status if the diet is continued for more than a few weeks without added minerals and vitamins.

The basic rice diet outlined by Kempner in the *North Carolina Medical Journal* (February, 1945) consists of 400 gm. of rice, fruit, fruit juices and sugar. It furnishes about 2000 calories, 20 gm. of protein, 0.2 gm. of chloride and 0.15 gm. of sodium. The following minimal doses are recommended: vitamin A, 500 units; vitamin D, 1000 units; thiamine chloride, 5 mg.; riboflavin, 5 mg.; niacinamide, 25 mg.; calcium pantothenate, 2 mg.; and ferrous sulfate, 0.6 mg. Without this supplementation the meals of rice and fruit tend to be low not only in protein but also in many of the minerals and vitamins. Such a diet when calculated shows itself to be adequate in vitamin A only provided prunes, apricots or peaches are used daily; high in vitamin C when orange and grapefruit juices are used; and low in calcium, protein and components of the vitamin B complex, particularly riboflavin. Sufficient iron is not supplied unless apricots and prunes are consumed regularly. Some physicians include 8 ounces of prune juice daily to meet the need of iron. If pineapples, apples, grapes (or their juices) or pears and bananas are substituted, in whole or in part, for the above fruits, the vitamin A, ascorbic acid and iron will fall below recommended levels.

The following menu is an example of a day's diet planned on Kempner's basic diet, and Table 1 shows how a day's rice diet, with these fruits, compares with the day's needs for a moderately active man.

BREAKFAST (7 A.M.)	LUNCH (11 A.M.)
1 cup orange juice 2 cups boiled rice 22 grapes	2 tablespoonsful honey on 3 cups rice 1 cup orange juice 2 fresh peaches
SUPPER (4 P.M.)	**NIGHT (8 P.M.)**
Rice crown 2 apricots (2 cups rice 4 stewed apricot halves) 1 cup prune juice ½ cantaloupe	1 cup orange juice 3 plums

TABLE 1. *Daily Requirements of a Moderately Active Man Weighing 70 kg.*

DAILY INTAKE	CALORIES	PROTEIN	CALCIUM	PHOSPHORUS	IRON	VITAMIN A	THIAMINE CHLORIDE	ASCORBIC ACID	RIBOFLAVIN
		gm.	*gm.*	*gm.*	*mg.*	*I. U.*	*mg.*	*mg.*	*mg.*
Ordinary diet.....	3000	70.0	0.8	0.88	12.0	5000	1.5	75	2.0
Diet with white rice .	1874	31.6	0.337	0.587	11.3	13,870	1.13	388	0.54
Diet with brown rice	1909	28.8	0.421	1.175	24.1	13,870	1.78	388	0.64

Both brown and white rice are recommended in rice diets. The above calculations do not take into account losses of thiamine, riboflavin and niacin that result from washing of rice. Such losses vary according to the rigor of the washing. They may be as high as 43 per cent of thiamine, 25 per cent of riboflavin and 23 per cent of niacin. Further losses result in cooking, but the most serious losses are due to washing. This will not be of importance if the diet is supplemented adequately, but may be of considerable consequence if the patient on the very restricted form of the diet makes a poor choice of fruits and overwashes the rice during preparation.

This particular day's diet includes both prunes and apricots and so provides a good amount of iron. The yellow foods, peaches, apricots, oranges

and the deeper-colored variety of cantaloupe make the diet more than adequate in vitamin A. However, calories, protein, calcium and riboflavin are very low, and wherever diets are low in calcium and protein they tend also to be low in phosphorus. The lowered calorie intake may need attention when an inactive patient returns to active work.

That protein restriction has a beneficial effect in hypertension has not yet been conclusively shown. This protein deficiency of the rice diet is being studied, and in some cases a form of low-sodium milk is in use to compensate for the deficiency of both protein and calcium.

MASSACHUSETTS TICK SURVEY

JOHN C. AYRES, M.D.,* AND
ROY F. FEEMSTER, M.D., DR.P.H.†

For many years, the wood tick, officially known as the American dog tick, has been an annual nuisance on Cape Cod and Martha's Vineyard and inland from the South Shore. In recent years, a few cases of such tick-borne diseases as Rocky Mountain spotted fever and tularemia have been occurring in the same area.

The Department was directed by Chapter 36 of the *Resolves* of 1948 to study the problem and seek to find ways by which the nuisance could be abated.

It is important, in connection with this study, to know the geographic distribution of this tick (*Dermacentor variabilis*) as well as any other important species of ticks with which it might be confused.

For the benefit of physicians who might like further information regarding the problem, a brief account of the ticks found in the State follows. Much of this information is taken from a voluminous compilation by Bequaert.[1]

Varieties

Ticks are divided into two families: the *Argasidae* or soft ticks and the *Ixodidae* or hard ticks. The former are more primitive and less constantly parasitic, produce fewer offspring, feed frequently and at night, do not increase greatly in size when gorged on blood and seldom travel far; the latter are more specialized and more highly parasitic, produce more numerous offspring, and take only one blood meal in each stage but are capable of taking such great quantities that they increase many times in size and weight. The hard ticks possess a horny shield, which entirely covers the back in the male and partially covers it in the female.

Prevalence

Of the four species of *Argasidae* found in the United States none is present in Massachusetts. On the other hand, several species of the *Ixodidae* are present. These are the common wood or dog tick (*D. variabilis*), which attacks dog and man and which feeds to a large extent in the immature stages on small rodents such as meadow mice; the rabbit ticks (*Haemaphysalis leporis palustris* and *Ixodes dentatus*), which do not attack man but which are often present in large numbers on rabbits and may also be found on meadow larks, quail and other birds; the mouse ticks (*Ixodes scapularis*, *Ixodes muris*), which are rather common on meadow mice, other small rodents and more rarely on rabbits; and other ticks (*Ixodes bruneus*, *I. cookei*, *I. marxi* and *Haemaphysalis chordeilis*,) which infest small animals and birds primarily.

D. variabilis is the most important one of this group since it is found regularly on dogs and frequently on human beings. It is a three-host tick. The fertilized female drops 2000 to 8000 eggs on the ground. In one or two months the eggs hatch, and the larvae attach themselves to small mammals and engorge for two to eight days. Then they drop to the ground, digest their meal and molt to nymphs. The first winter they usually spend as unfed nymphs. The following spring the nymphs attach themselves to rodents, engorge, drop to the ground, digest their meal and molt to adults. The unfed adults attach themselves to larger mammals, including man, mate, engorge and drop off.

The distribution of ticks in areas depends upon the presence of hosts. The meadow mouse is the principal host of the young forms, and the best "mouse country" is uncut, ungrazed grassland dotted with variable amounts of thickets and shrubs. Beach grass, grassy patches in woodland, and areas denuded in lumbering are also favorable, but ticks are seldom found in forests.

Ticks As Transmitters of Disease

Ticks have been recognized as transmitters of disease in man and animals since 1893. Many species not only carry disease-producing organisms through several stages of change in form but also transmit them through the eggs to the next generation. They transmit five groups of disease: rickettsial, viral, bacterial, spirochetal and protozoan. In America, ticks have been proved to be transmitters of Rocky Mountain spotted fever, tularemia, Q fever and Colorado tick fever and to cause tick paralysis by a poisonous substance that they produce. Furthermore, in the laboratory they have been shown to be capable of transmitting other diseases, such as encephalitis.

Ticks obtain micro-organisms from their various hosts. These organisms in turn develop within the tick, invading all tissues and passing through all stages finally to the egg. Once the tick is infected it can transmit the disease to other animals, birds, rodents and even man. The newly infected hosts then act as new reservoirs for other uninfected

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†Director, Division of Communicable Diseases, Massachusetts Department of Public Health.

ticks and so a vicious circle is formed, spreading and perpetuating the disease.

In Massachusetts, ticks have been known to spread only tularemia and Rocky Mountain spotted fever. Tularemia made its first appearance in Massachusetts in 1937 in Falmouth, and a total of 17 cases had been reported to the Department of Public Health up to and including 1947. Ten of the 17 cases occurred in the tick-infested area and were attributed to tick bites. On the other hand, Rocky Mountain spotted fever first made its appearance in 1938 in Dennis; 10 cases have been reported, 2 being contracted outside Massachusetts and the remaining 8 in the tick area of the Cape. The problem of tularemia in Massachusetts has recently been discussed in detail in the *Journal*.[2]

Although it is important to attempt to control ticks in Massachusetts because of the possibility of their transmitting certain diseases, the most pressing reason for such control is the fact that they are a trying nuisance. In the southeastern portion of the Commonwealth, every spring and summer, residents and visitors in the area must perform the daily task of inspecting themselves and members of their families for the presence of ticks and must frequently perform the tedious chore of removing ticks from dogs and other pets.

The study was started too late this year to permit much information to be accumulated regarding the control of ticks by sprays. A few experiments have confirmed observations of others that the prevalence of ticks can be decreased by spraying of the grass and bushes in an infested area with DDT. Unfortunately, such a measure is only palliative and probably only affects in a minor way the eventual solution of the problem, because it is feasible to spray only restricted areas that are most frequented by residents and summer visitors and their dogs. Reproduction of ticks is continued because dogs wander into areas of lower prevalence and furnish the blood meals for ticks that will replenish the tick population.

If spraying operations could be supplemented by measures to keep ticks from obtaining their blood meals from dogs, a much more permanent effect could be obtained.

It is expected that the tick study will be continued for the next year or two so that some of these problems can be attacked. Dipping dogs is usually much more effective in getting rid of ticks, but the operation is messy and dog owners will not take advantage of this method of control. A thorough study of the usefulness of DDT, rotenone and other materials in powder form would be useful.

Any assistance that physicians can give to increase knowledge of the geographic distribution of the tick population will be useful in the study. In the August 26 issue of the *Journal*, a questionnaire, which is being used for accumulating information, was referred to. Any physicians who did not fill out the form are asked to forward it with any information which is available.

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CORRESPONDENCE

FURTHER DATA ON LOWER-NEPHRON AND MERCURIAL NEPHROSIS

To the Editor: It is believed that the following addendum to my paper on "Acute Renal Insufficiency Due to Lower-Nephron Nephrosis," which appeared in the November 4 issue of the *Journal*, will be of interest:

The pathologic lesion in mercurial nephrosis differs from that of lower-nephron nephrosis in that the proximal segment of the convoluted tubule is chiefly affected. The following case is of interest because, as pointed out by R. Batson and J. C. Peterson, in an article entitled "Acute Mercury Poisoning: Treatment with BAL in anuric states with continuous peritoneal lavage" (*Ann. Int. Med.* **29**:278-293, 1948), it is currently believed that ". . . these patients who, not having received BAL therapy within the first few hours, will develop anuria secondary to tubular injury. These patients will ultimately die unless something can be done to provide a temporary means of controlling their uremia until renal function returns."

This case illustrates that the general principles originally put forth by J. P. Peters, A. J. Eisenman and D. M. Kydd, in an article entitled "Mercury Poisoning" (*Am. J. M. Sc.* **185**:149-171, 1933) remain sound.

A 48-year-old mechanical engineer (B. C. H. 1298442) accidentally ingested 0.5 to 1.0 gm. of mercuric bichloride on the morning of September 22, after which he had breakfast and then became nauseated, vomiting at first food and then bloody material. Shortly thereafter watery bloody diarrhea began. During the 8 hours prior to hospitalization he vomited five or six times, had at least ten watery, red stools and passed urine several times. On entry there was very mild evidence of shock. The hematocrit was 57 per cent, the hemoglobin 18 gm. per 100 cc., and the white-cell count 28,000. Shortly after admission he received an intravenous infusion of 500 cc. of physiologic saline solution followed by 500 cc. of citrated whole blood. Early the next morning the same quantity of blood and saline solution was administered. Since the hematocrit remained at 50 per cent in spite of this therapy 1000 cc. of 10 per cent glucose in saline solution was given, after which the hematocrit declined to 44 per cent and the hemoglobin to 15 gm. Shortly after admission the patient voided 200 cc. urine, which gave a ++++ test for albumin, with many casts and occasional white and red cells in the sediment. Nine days later 50 cc. of urine appeared. During the period of anuria the patient received approximately 750 cc. of 15 per cent of glucose in distilled water daily, as well as intravenous injections of an amount of physiologic saline solution or its equivalent as sodium bicarbonate or sodium lactate equal to the output in vomitus or stool.

Forty-eight hours after entry stool examinations were reported as positive for mercury (the patient up till this time had steadfastly denied the possibility of poisoning of any type). He therefore received 1575 mg. of BAL intramuscularly divided into nine equal doses during the next 48 hours. With the omission of all liquids and food by mouth, vomiting ceased promptly. Within a few days there was no further diarrhea. The temperature, pulse, respirations and blood pressure showed no essential change. The blood nonprotein nitrogen rose to a peak of 252 mg. per 100 cc. on the 13th day. The serum sodium remained at approximately 133 milliequiv. per liter. The serum potassium, which was 4.6 milliequiv. per liter on the 3rd day, never rose above 5 milliequiv. The

serum chloride declined to a low of 68 milliequiv., and the carbon dioxide to 9.9 milliequiv. per liter. On the 9th day 50 cc. of urine was passed, followed on successive days by 100, 260, 500, 1000, 2000 and 3300 cc. This urinary output was associated with a falling nonprotein nitrogen and a rise in serum chloride and carbon dioxide. With the urine output at 2000 cc. the patient was allowed fluids and food freely by mouth and made an uneventful recovery. He returned to work 24 days after the onset of illness.

Since my manuscript was submitted for publication, gastric and intestinal lavage has been successfully employed in the treatment of 7 patients with uremia associated with prostatism, by V. Vermooten and D. M. Hare reported in an article entitled "The Use of Continuous Gastric Lavage in the Treatment of Uremia Associated with Prostatism" (*J. Urol.* **59**:907-919, 1948), and in a patient with anuria and uremia secondary to the ingestion of cleaning fluid by H. H. Marquis and F. P. Schnell as noted in a report entitled "The Treatment of Anuria by Intestinal Perfusion" (*Am. J. M. Sc.* **215**:686-693, 1948). In this case, no attempt was made to follow the level of serum potassium until cardiac arrhythmia appeared, when it was found to be 1.2 milliequiv. per liter, or approximately a fourth normal. Death appeared to have been caused by this extreme hypopotassemia.

MAURICE B. STRAUSS, M.D.
Chief of Medical Service

Cushing Veterans Administration Hospital
Framingham, Massachusetts.

NOTICES

ANNOUNCEMENT

Dr. Carl V. Lendgren announces the removal of his office to 8195 California Avenue, South Gate, California.

SOUTH BOSTON MEDICAL SOCIETY

A meeting of the South Boston Medical Society will be held on Monday, November 15, at 9 p.m., at the Carney Hospital. Dr. Grantley W. Taylor will speak on the subject "Oral Carcinoma."

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held at the Boston Medical Library on Tuesday, November 16, at 8:15 p.m. A symposium entitled "Recent Advances in the Diagnosis and Treatment of Psychiatric Disorders" will be presented, with Dr. Harry C. Solomon as chairman.

PROGRAM

Lobotomy. Dr. James Poppen.

Current Somatic Therapies in Psychiatry. Dr. Milton Greenblatt.

Psychotherapy: Illustrated by dermatologic cases. Dr. Lester L. Hasenbush.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 16, at 12 noon. The speaker will be Dr. William J. Mulligan, who will discuss the subject, "Disorders of Menstruation."

Physicians are cordially invited to attend.

BOSTON STATE HOSPITAL PSYCHIATRIC SEMINAR SCHEDULE

Psychiatric seminars will be held in the Reception Auditorium of the Boston State Hospital during 1948-1949 on Wednesdays at 12 noon, followed by a staff luncheon at 1 p.m.

SCHEDULE

1948

November 17. The Electroencephalogram in Psychiatric Research. Dr. Robert S. Schwab.

November 24. The Work of the Psychologist in Relation to Psychiatry. Dr. Herbert I. Harris.

December 1. Psychotherapy for Psychosomatic Disorders. Dr. Grete L. Bibring.

December 8. Care of the Disturbed Psychotic Patient. (To be announced.)

December 15. Teaching Psychotherapy in an Outpatient Department. Dr. Bernard Bandler.

December 22. A Theory of Personality. Dr. Andras Angyal.

December 29. Mongolian Idiocy. Dr. Clemens Banda.

1949

January 5. What Society Should Do for the Alcoholic. (To be announced.)

January 12. The Neurological Basis of the Emotions. Dr. Stanley Cobb.

January 19. (To be announced.)

January 26. Recent Developments in the Treatment of Epilepsy. Dr. Harry Kozol.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A meeting of the Boston Society of Psychiatry and Neurology will be held at the Boston Medical Library, 8 Fenway, on Thursday, November 18, at 8:15 p.m.

PROGRAM

Acoustic Tumors: Intracapsular removal versus total resection. Gilbert Horrax, M.D. Lantern slides (thirty minutes).

Psychometric Changes after Lobotomy. Charles A. Atwell, M.A. (fifteen minutes).

Sexual Behavior after Lobotomy. Julius Levine, M.D., and Harold Albert, M.D. (fifteen minutes).

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the Anesthesia Study Committee of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, on Tuesday, November 23, at 8 p.m. The chairman will be Dr. Meyer Saklad. There will be a presentation of case reports on morbidity and mortality, followed by a discussion from the floor.

Physicians and medical students are invited to attend.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs in its evening lecture series.

November 16. Practice Inside and Outside the Hospital. Dr. Samuel A. Levine.

November 23. Hypertension as a Disease of Adaptation. Dr. Hans Selye, professor and director of the Institute of Experimental Medicine and Surgery, University of Montreal Faculty of Medicine.

November 30. Physiology of the Liver, and Liver-Function Tests. Dr. Franklin M. Hanger, Jr., associate professor of medicine, Columbia University College of Physicians and Surgeons and associate attending physician, Presbyterian Hospital, New York City.

These programs are held at 7 p.m. in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital.

All interested persons are invited to attend.

(*Notices concluded on page xvii*)